
20
years
of
AIDS

A foreword by John Ward, M.D.

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Twenty years ago, on June 5, 1981, the Centers for Disease Control and Prevention's (CDC's) flagship publication, the *Morbidity and Mortality Weekly Report* (*MMWR*), reported five cases of *Pneumocystis carinii* pneumonia affecting young gay men in Los Angeles; two of the men had died. At the time, it seemed an anomaly, of possible interest only to a handful of public health and medical professionals. We know today that this brief article heralded the onset of a global epidemic of a disease now called AIDS that has caused hundreds of thousands of deaths around the world and affected millions more.

Since that time, the *MMWR* has published over 400 reports about AIDS — a chronicle of the understanding, transmission, prevention, and therapy of the disease. This chronicle shows a disease that rapidly gained momentum, both in numbers and in range. The early reports (1981, 1982, 1983) are milestones in an era of discovery and awareness when prevention recommendations were made based solely on epidemiologic studies before the cause of the new, unexplained illness was known. During this time, the *MMWR* became a primary source of information about the spread of AIDS, prevention, and care.

Shortly following the identification of the retrovirus that causes AIDS (1984), now known as the human immunodeficiency virus (HIV), a blood test to detect the antibodies to HIV (1985) was developed. This advance helped researchers discover that persons who had developed AIDS were only the "tip of the iceberg" of a much larger epidemic of HIV infection. The advent of HIV antibody testing ushered in an era of new prevention interventions to further protect the Nation's blood supply (1985) and prevent transmission to newborns (1985), and to help people learn their infection status and how to protect others (1987). These expanded prevention efforts introduced the concept of universal precautions for health care workers (1987) and general education to promote healthy behaviors among target populations such as youth (1988). Use of the antibody test also improved tracking of the disease and clinical diagnosis for treatment of tuberculosis and other AIDS-related diseases (1987; 1992).

Following the approval of azidothymidine (AZT, zidovudine) in 1987, clinical trials in the 1990s showed this treatment to be effective in prevention of perinatal transmission of HIV. The *MMWR* published guidelines for the widespread use of AZT among pregnant women with HIV (1994). As a result, AIDS among newborns has become a rarity in the United States, making elimination of this mode of transmission a reachable goal (2001). In 1996, a milestone in the fight against AIDS was reached with the development of new, highly effective antiretroviral therapies. Although not a cure, these treatments, used in combination therapy, delayed illness and death among persons infected with HIV (1997). AIDS cases and deaths soon began to decline (1997) and new guidelines for care (1995) and treatment for persons with HIV (1998) were published.

The June 1, 2001, issue of *the MMWR* — Twenty Years of AIDS — provides updated information about the ongoing epidemiologic aspects and impact of HIV/AIDS on communities in the United States and other countries. The issue contains the recurring message that calls for vigorous and renewed efforts to respond to the continuing devastation of AIDS (2001).

The *MMWR* collection contained within is more than a historical account. It is an important and impressive chronicle of the first 20 years of the HIV/AIDS epidemic and the tireless efforts of hundreds of people in various fields — science, medicine, prevention, labor, legal, social, behavioral, and many other professionals and volunteers — who have worked to end the spread of this disease in the world. As the pandemic of HIV evolves and new prevention strategies and treatments are developed, the *MMWR* will continue to be at the forefront to produce timely and critical reports about HIV infection and AIDS.

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1981 June 5;30:250–2

Pneumocystis Pneumonia – Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with elevated liver enzymes, leukopenia, and CMV viruria. The serum complement-fixation CMV titer in October 1980 was 256; in May 1981 it was 32.* The patient's condition deteriorated despite courses of treatment with trimethoprim-sulfamethoxazole (TMP/SMX), pentamidine, and acyclovir. He died May 3, and postmortem examination showed residual *P. carinii* and CMV pneumonia, but no evidence of neoplasia.

Patient 2: A previously healthy 30-year-old man developed *P. carinii* pneumonia in April 1981 after a 5-month history of fever each day and of elevated liver-function tests, CMV viruria, and documented seroconversion to CMV, i.e., an acute-phase titer of 16 and a convalescent-phase titer of 28* in anticomplement immunofluorescence tests. Other features of his illness included leukopenia and mucosal candidiasis. His pneumonia responded to a course of intravenous TMP/SMX, but, as of the latest reports, he continues to have a fever each day.

Patient 3: A 30-year-old man was well until January 1981 when he developed esophageal and oral candidiasis that responded to Amphotericin B treatment. He was hospitalized in February 1981 for *P. carinii* pneumonia that responded to oral TMP/SMX. His esophageal candidiasis recurred after the pneumonia was diagnosed, and he was again given Amphotericin B. The CMV complement-fixation titer in March 1981 was 8. Material from an esophageal biopsy was positive for CMV.

Patient 4: A 29-year-old man developed *P. carinii* pneumonia in February 1981. He had had Hodgkins disease 3 years earlier, but had been successfully treated with radiation therapy alone. He did not improve after being given intravenous TMP/SMX and corticosteroids and died in March. Postmortem examination showed no evidence of Hodgkins disease, but *P. carinii* and CMV were found in lung tissue.

Patient 5: A previously healthy 36-year-old man with a clinically diagnosed CMV infection in September 1980 was seen in April 1981 because of a 4-month history of fever, dyspnea, and cough. On admission he was found to have *P. carinii* pneumonia, oral candidiasis, and CMV retinitis. A complement-fixation CMV titer in April 1981 was 128. The patient has been treated with 2 short courses of TMP/SMX that have been limited because of a sulfa-induced neutropenia. He is being treated for candidiasis with topical nystatin.

The diagnosis of *Pneumocystis* pneumonia was confirmed for all 5 patients antemortem by closed or open lung biopsy. The patients did not know each other and had no known common contacts or knowledge of sexual partners who had had similar illnesses. The 5 did not have comparable histories of sexually transmitted disease. Four had serologic evidence of past hepatitis B infection but had no evidence of current hepatitis B surface antigen. Two of the 5 reported having frequent homosexual contacts with various partners. All 5 reported using inhalant drugs, and 1 reported parenteral drug abuse. Three patients had profoundly depressed numbers of thymus-dependent lymphocyte cells and profoundly depressed *in vitro* proliferative responses to mitogens and antigens. Lymphocyte studies were not performed on the other 2 patients.

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Editorial Note: *Pneumocystis* pneumonia in the United States is almost exclusively limited to severely immunosuppressed patients (*1*). The occurrence of pneumocystosis in these 5 previously healthy individuals without a clinically apparent underlying immunodeficiency is unusual. The fact that these patients were all homosexuals suggests an association between some aspect of a homosexual lifestyle or disease acquired through sexual contact and *Pneumocystis* pneumonia in this population. All 5 patients described in this report had laboratory-confirmed CMV disease or virus shedding within 5 months

*Paired specimens not run in parallel.

of the diagnosis of *Pneumocystis* pneumonia. CMV infection has been shown to induce transient abnormalities of *in vitro* cellular-immune function in otherwise healthy human hosts (*2,3*). Although all 3 patients tested had abnormal cellular-immune function, no definitive conclusion regarding the role of CMV infection in these 5 cases can be reached because of the lack of published data on cellular-immune function in healthy homosexual males with and without CMV antibody. In 1 report, 7 (3.6%) of 194 patients with pneumocystosis also had CMV infection; 40 (21%) of the same group had at least 1 other major concurrent infection (*1*). A high prevalence of CMV infections among homosexual males was recently reported: 179 (94%) of 190 males reported to be exclusively homosexual had serum antibody to CMV, and 14 (7.4%) had CMV viruria; rates for 101 controls of similar age who were reported to be exclusively heterosexual were 54% for seropositivity and zero for viruria (*4*). In another study of 64 males, 4 (6.3%) had positive tests for CMV in semen, but none had CMV recovered from urine. Two of the 4 reported recent homosexual contacts. These findings suggest not only that virus shedding may be more readily detected in seminal fluid than in urine, but also that seminal fluid may be an important vehicle of CMV transmission (*5*).

All the above observations suggest the possibility of a cellular-immune dysfunction related to a common exposure that predisposes individuals to opportunistic infections such as pneumocystosis and candidiasis. Although the role of CMV infection in the pathogenesis of pneumocystosis remains unknown, the possibility of *P. carinii* infection must be carefully considered in a differential diagnosis for previously healthy homosexual males with dyspnea and pneumonia.

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Epidemiologic Notes and Reports Pneumocystis carinii Pneumonia among Persons with Hemophilia A

CDC recently received reports of three cases of Pneumocystis carinii pneumonia among patients with hemophilia A and without other underlying disease. Two have died; one remains critically ill. All three were heterosexual males; none had a history of intravenous (IV) drug abuse. All had lymphopenia, and the two patients who were specifically tested have had in vitro laboratory evidence of cellular immune deficiency. The case reports follow.

Patient 1: A 62-year-old resident of Westchester County, New York, with a history of chronic hepatitis had received frequent injections of Factor VIII concentrate for severe hemophilia for many years. In February 1981, he began to experience weight loss and vague right upper quadrant abdominal discomfort associated with laboratory evidence of increasing hepatic dysfunction. In December 1981, while hospitalized in Miami, Florida, for elective knee surgery, he complained of cough and fever. He was lymphopenic, and chest X-ray revealed interstitial infiltrates compatible with viral pneumonia. He was discharged in late December after a brief course of corticosteroids associated with overall clinical improvement. He returned in severe respiratory distress a few days later. Open lung biopsy on January 5 revealed P. carinii, for which he received sulfamethoxazole/trimethoprim (SMZ/TMP) during the 2 weeks before death. P. carinii pneumonia and micronodular cirrhosis were documented at post-mortem examination.

Patient 2: A 59-year-old lifelong resident of Denver, Colorado, noted the onset of gradual weight loss, dysphagia associated with pharyngitis, aphthous-like ulcers, and anterior cervical adenopathy beginning in October 1980. As a patient with severe hemophilia, he had received frequent injections of Factor VIII concentrate for several years. Weight loss continued over a period of months. Oropharyngeal candidiasis was diagnosed in February 1982. He was hospitalized in May 1982 with symptoms including nausea, vomiting, and recurrent fever. Pneumonia was diagnosed, and P. carinii and cytomegalovirus (CMV) were repeatedly identified from lung tissue or bronchial secretions using histopathologic and culture techniques. Therapy with SMZ/TMP and pentamidine isethionate continued until death on July 5, 1982. Laboratory evidence for cellular immune dysfunction included absent mitogen responses and depletion of the T-helper lymphocyte cell population, relative increase in T-suppressor cells, and resultant inverted T-helper/T-suppressor ratio.

Patient 3: A previously healthy 27-year-old lifelong resident of northeastern Ohio developed fever, urinary frequency and urgency, and extreme lassitude in July 1981. He had frequently received parenteral Factor VIII concentrate for severe hemophilia. Bilateral pneumonia was diagnosed in October 1981, and open lung biopsy revealed P. carinii. He responded successfully to a 3-week course of SMZ/TMP. In February 1982, he received ketoconazole to suppress repeated episodes of oral candidiasis. He was hospitalized again in April with fever, splenomegaly, anemia, and

lymphopenia. An extensive tumor work-up (including laparotomy) did not uncover an underlying malignancy. Cultures of bone marrow, liver, mesenteric lymph nodes, and blood grew Mycobacterium avium. In vitro immunological testing in March indicated a reduction in absolute number of circulating T-cells. Subsequent, more extensive testing documented the lack of lymphocyte responsiveness to mitogens, absolute and relative decrease in T-helper cells, relative increase in T-suppressor cells, and resultant inverted T-helper/T-suppressor ratio.

For each patient, records of the administration of Factor VIII concentrate were reviewed to determine manufacturer and lot numbers. No two of the patients are known to have received concentrate from the same lots. Reported by: NJ Ehrenkranz, MD, South Florida Hospital Consortium for Infection Control, J Rubini, MD, Cedars of Lebanon Hospital, Miami, R Gunn, MD, State Epidemiologist, Florida Dept of Health and Rehabilitative Svcs; CR Horsburgh, MD, T Collins, MD, U Hasiba, MD, W Hathaway, MD, University of Colorado School of Medicine, W. Doig, MD, R Hopkins, MD, State Epidemiologist, Colorado Dept of Health; J Elliott, MD, W Hoppes, MD, I Patel, MD, Aultman Hospital, Canton, CE Krill, MD, Children's Hospital, Akron, T Halpin, MD, State Epidemiologist, Ohio Dept of Health; Field Services Div, Epidemiology Program Office, Div of Host Factors, Center for Infectious Diseases, Task Force on Kaposi's Sarcoma and Opportunistic Infections, CDC.

Editorial Note

Editorial Note: Pneumocystis carinii pneumonia has not been previously reported among hemophilia patients who have had no other underlying diseases and have not had therapy commonly associated with immunosuppression. A review of the Parasitic Disease Drug Service's records of requests for pentamidine isethionate for 1980-1982 failed to identify hemophilia among the underlying disorders of patients for whom pentamidine was requested for Pneumocystis carinii therapy.

The clinical and immunologic features these three patients share are strikingly similar to those recently observed among certain individuals from the following groups: homosexual males, heterosexuals who abuse IV drugs, and Haitians who recently entered the United States.(1-3) Although the cause of the severe immune dysfunction is unknown, the occurrence among the three hemophiliac cases suggests the possible transmission of an agent through blood products.

Hemophilia A is a sex-linked, inherited disorder characterized by a deficiency in Factor VIII activity. There are an estimated 20,000 patients with hemophilia A in the United States (4). Severity of disease is classified according to percentage of endogenous Factor VIII activity. Approximately 60% of the 20,000 are classified as severe, and 40% are classified as moderate (4). Factor VIII deficiency can be treated with intravenous administration of exogenous Factor VIII as either cryoprecipitate made from individual units of fresh frozen plasma or lyophilized Factor VIII concentrate manufactured from plasma pools collected from as many as a thousand or more donors.

CDC has notified directors of hemophilia centers about these cases and, with the National Hemophilia Foundation, has initiated collaborative surveillance. A Public Health Service advisory committee is being formed to consider the implication of these findings. Physicians diagnosing opportunistic infections in hemophilia patients who have not received antecedent immunosuppressive therapy are encouraged to report them to the CDC through local and state health departments.

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Epidemiologic Notes and Reports Possible Transfusion-Associated Acquired Immune Deficiency Syndrome (AIDS) -- California

CDC has received a report of a 20-month old infant from the San Francisco area who developed unexplained cellular immunodeficiency and opportunistic infection. This occurred after multiple transfusions, including a transfusion of platelets derived from the blood of a male subsequently found to have the acquired immune deficiency syndrome (AIDS).

The infant, a white male, was delivered by caesarian section on March 3, 1981. The estimated duration of pregnancy was 33 weeks; and the infant weighed 2850 g. The mother was known to have developed Rh sensitization during her first pregnancy, and amniocentesis done during this, her second, pregnancy showed the fetus had erythroblastosis fetalis. The infant had asphyxia at birth and required endotracheal intubation. Because of hyperbilirubinemia, six double-volume exchange transfusions were given over a 4-day period. During the 1-month hospitalization following birth, the infant received blood products, including whole blood, packed red blood cells, and platelets from 19 donors. All blood products were irradiated.

After discharge in April 1981, the infant appeared well, although hepatosplenomegaly was noted at age 4 months. At 7 months, he was hospitalized for treatment of severe otitis media. Oral candidiasis developed following antibiotic therapy and persisted. At 9 months of age, he developed anorexia, vomiting, and then jaundice. Transaminase levels were elevated, and serologic tests for hepatitis A and B viruses and cytomegalovirus were negative; non-A non-B hepatitis was diagnosed.

At 14 months of age, the infant developed neutropenia and an autoimmune hemolytic anemia and thrombocytopenia. Immunologic studies showed elevated serum concentrations of IgG, IgA, and IgM, decreased numbers of T-lymphocytes, and impaired T-cell function in vitro. Following these studies, he was begun on systemic corticosteroid therapy for his hematologic disease. Three months later, a bone marrow sample, taken before steroid therapy began, was positive for Mycobacterium avium-intracellulare. Cultures of urine and gastric aspirate, taken while the infant received steroids, also grew M. avium-intracellulare. The infant is now receiving chemotherapy for his mycobacterial infection. He continues to have thrombocytopenia.

The parents and brother of the infant are in good health. The parents are heterosexual non-Haitians and do not have a history of intravenous drug abuse. The infant had no known personal contact with an AIDS patient.

Investigation of the blood products received by the infant during his first month of life has revealed that one of the 19 donors was subsequently reported to have AIDS. The donor, a 48-year-old white male resident of San Francisco, was in apparently good health when he donated blood on March 10,

1981. Platelets derived from this blood were given to the infant on March 11. Eight months later, the donor complained of fatigue and decreased appetite. On examination, he had right axillary lymphadenopathy, and cotton-wool spots were seen in the retina of the left eye. During the next month, December 1981, he developed fever and severe tachypnea and was hospitalized with biopsy-proven Pneumocystis carinii pneumonia.

Although he improved on antimicrobial therapy and was discharged after a 1-month hospitalization, immunologic studies done in March 1982 showed severe cellular immune dysfunction typical of AIDS. In April 1982, he developed fever and oral candidiasis, and began to lose weight. A second hospitalization, beginning in June 1982, was complicated by Salmonella sepsis, perianal herpes simplex virus infection, encephalitis of unknown etiology, and disseminated cytomegalovirus infection. He died in August 1982. Reported by A Ammann, MD, M Cowan, MD, D Wara, MD, Dept of Pediatrics, Univeristy of California at San Francisco, H Goldman, MD, H Perkins, MD, Irwin Memorial Blood Bank, R Lanzerotti, MD, J Gullett, MD, A Duff, MD, St. Francis Memorial Hospital, S Dritz, MD, City/County Health Dept, San Francisco, J Chin, MD, State Epidemiologist, Calfornia State Dept. of Health Svcs; Field Svcs Div, Epidemiology Program Office, AIDS Activity, Div of Host Factors, Center for Infectious Diseases, CDC.

Editorial Note

Editorial Note: The etiology of AIDS remains unknown, but its reported occurrence among homosexual men, intravenous drug abusers, and persons with hemophilia A (1) suggests it may be caused by an infectious agent transmitted sexually or through exposure to blood or blood products. If the infant's illness described in this report is AIDS, its occurrence following receipt of blood products from a known AIDS case adds support to the infectious-agent hypothesis.

Several features of the infant's illness resemble those seen among adults with AIDS. Hypergammaglobulinemia with T-cell depletion and dysfunction are not typical of any of the well-characterized congenital immunodeficiency syndromes (2), but are similar to abnormalities described in AIDS (3). Disseminated M. avium-intracellulare infection, seen in this infant, is a reported manifestation of AIDS (4). Autoimmune thrombocytopenia, also seen in this infant, has been described among several homosexual men with immune dysfunction typical of AIDS (5). Nonetheless, since there is no definitive laboratory test for AIDS, any interpretation of this infant's illness must be made with caution.

If the platelet transfusion contained an etiologic agent for AIDS, one must assume that the agent can be present in the blood of a donor before onset of symptomatic illness and that the incubation period for such illness can be relatively long. This model for AIDS transmission is consistent with findings described in an investigation of a cluster of sexually related AIDS cases among homosexual men in southern California (6).

Of the 788 definite AIDS cases among adults reported thus far to CDC, 42 (5.3%) belong to no known risk group (i.e., they are not known to be homosexually active men, intravenous drug abusers, Haitians, or hemophiliacs). Two cases received blood products within 2 years of the onset of their illnesses and are currently under investigation.

This report and continuing reports of AIDS among persons with hemophilia A (7) raise serious questions about the possible transmission of AIDS through blood and blood products. The Assistant Secretary for Health is convening an advisory committee to address these questions.

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MMWR Weekly December 17, 1982 / 31(49);665-667

Unexplained Immunodeficiency and Opportunistic Infections in Infants -- New York, New Jersey, California

CDC has received reports of four infants (under 2 years of age) with unexplained cellular immunodeficiency and opportunistic infections.

Case 1: The infant, a black/hispanic male weighing 5 lb 14 oz, was born in December 1980 following a 36-38-week pregnancy. Pregnancy had been complicated by bleeding in the fourth month and by preeclampsia in the ninth month. The infant was well until 3 months of age, when oral candidiasis was noted. At 4 months, hepatosplenomegaly was observed, and at 7 months, he had staphylococcal impetigo. Growth, which had been slow, stopped at 9 months. Head circumference, which had been below the third percentile, also stopped increasing. At 9 months, serum levels of IgG and IgA were normal; IgM was high-normal. T-cell studies were normal, except for impaired in-vitro responses to Candida antigen and alloantigen.

At 17 months of age, the infant had progressive pulmonary infiltrates, as well as continuing oral candidiasis, and was hospitalized. Mycobacterium avium-intracellulare was cultured from sputum and bone marrow samples. A CAT scan of the head revealed bilateral calcifications of the basal ganglia and subcortical regions of the frontal lobes. Repeat immunologic studies done at age 20 months showed lymphopenia, decreased numbers of T-lymphocytes, and severely impaired T-cell function in vitro; immunoglobulin determinations are pending. The infant remains alive and is receiving therapy for his mycobacterial infection.

The infant's mother, a 29-year-old resident of New York City, gave a history of intravenous drug abuse. Although she was in apparently good health at the time of the infant's birth, she developed fever, dyspnea, and oral candidiasis in October 1981. One month later, she was hospitalized and died of biopsy-proven Pneumocystis carinii pneumonia (PCP). She had been lymphopenic during the hospitalization; further immunologic studies were not done. At autopsy, no underlying cause for immune deficiency was found.

Case 2: The infant, a Haitian male weighing 6 lb 11 oz, was born in January 1981 following full-term pregnancy. The immediate postpartum period was complicated by respiratory distress. Diarrhea developed at 2 weeks of age and persisted. His physical development was retarded. At 5 months, he was hospitalized because of fever and diarrhea. On examination, he had hepatosplenomegaly, lymphadenopathy, and otitis media. While on antibiotics, he developed pulmonary infiltrates. An open lung biopsy revealed Pneumocystis carinii, Cryptococcus neoformans, and cytomegalovirus. Serum IgG, IgA, and IgM concentrations were elevated. The percentage of T-lymphocytes was decreased, but T-cell response to mitogens was normal. The infant died of respiratory insufficiency at 7H months of age. At autopsy, the thymus, spleen, and lymph nodes showed lymphocyte depletion.

His parents were residents of Brooklyn, New York; their health status is unknown.

Case 3: The infant, a Haitian male weighing 8 lb, was born in November 1981 following a normal, full-term pregnancy. He was apparently healthy until 5 months of age, when he was hospitalized with fever and respiratory distress. On examination, he had hepatosplenomegaly. A chest x-ray showed bilateral pulmonary infiltrates. Despite antibiotic therapy, the infant's condition deteriorated, and an open lung biopsy revealed PCP. Immunologic studies showed elevated serum concentrations of IgG, IgA and IgM, decreased percentage of T-lymphocytes, and impaired T-cell function in vitro. The infant died in May 1982. At autopsy, no cardiovascular anomalies were seen; the thymus was hypoplastic, but all lobes were present. His parents were residents of Newark, New Jersey; their health status is unknown.

Case 4: The infant, a white female weighing 5 lb, was born in April 1982 following a normal 35-week pregnancy. She was well until 2 months of age, when oral and vaginal Candida infections were noted. She responded to antifungal therapy, but at 5 months, candidiasis recurred, and she had hepatosplenomegaly. Immunologic evaluation showed that serum IgG, IgA, and IgM levels, normal at 2 months, were now elevated. The percentage of T-lymphocytes was decreased, and lymphocyte response to alloantigen was impaired. At 6 months of age, the infant was hospitalized because of fever and cough. Open lung biopsy revealed PCP. Despite appropriate antibiotic therapy, she died in November 1982.

The infant's mother, a 29-year-old resident of San Francisco, is a prostitute and intravenous drug abuser with a history of oral candidiasis and mild lymphopenia. She has had two other female children by different fathers. These half-sisters also have unexplained cellular immunodeficiency; one died of PCP. The children had not lived together.

None of the four infants described in the case reports was known to have received blood or blood products before onset of illness.

Other cases with opportunistic infections: Six additional young children with opportunistic infections (five with PCP, one with M. avium-intracellulare) and unusual cellular immunodeficiencies are under investigation. Three are male. All six children have died. One was a half-sister of the infant in Case 4.

Other cases without opportunistic infections: Physicians from New York City, New Jersey, and California have reported another 12 young children with immunodeficiencies similar to those seen in cases 1-4 but without life-threatening opportunistic infections. One is the other half-sister of the infant in Case 4. All the children are living; their ages range from 1 to 4 years. Eight are male. Clinical features seen in these 12 infants include: failure to thrive (83%), oral candidiasis (50%), hepatosplenomegaly (92%), generalized lymphadenopathy (92%), and chronic pneumonitis without a demonstrable infection (83%). Of the nine mothers for whom information is available, seven are reported to be intravenous drug abusers. None is Haitian. Reported by R O'Reilly, MD, D Kirkpatrick, MD, Memorial Sloan-Kettering Cancer Center, C Butkus Small, MD, R Klein, MD, H Keltz, MD, G Friedland, MD, Montefiore Hospital and Medical Center, K Bromberg, MD, S Fikrig, MD, H Mendez, MD, State University of New York, Downstate Medical Center, A Rubinstein, MD, Albert Einstein College of Medicine, M Hollander, MD, Misericordia Hospital Medical Center, F Siegal, MD, Mt Sinai School of Medicine, J Greenspan, MD, Northshore University Hospital, M Lange, MD, St Lukes-Roosevelt Hospital Center, S Friedman, MD, New York City Dept of Health, R Rothenberg, MD, State Epidemiologist, New York State Dept of Health; J Oleske, MD, C Thomas MD, R Cooper, MD, A de la Cruz, MD, St Michaels Medical Center, A Minefore, MD, St Josephs

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Editorial Note

Editorial Note: The nature of the immune dysfunction described in the four case reports is unclear. The infants lacked the congenital anomalies associated with Di George's syndrome. The immunologic features of high-normal or elevated immunoglobulin levels and T-lymphocyte depletion are not typical of any of the well-defined congenital immunodeficiency syndromes. They have, however, been described in a few children with variants of Nezelof's syndrome, a rare, poorly characterized illness of unknown etiology (1,2). The occurrence of immune deficiency in the infant in case 4 and in her half-sisters raises the possibility of an inherited disorder. However, inheritance would have to have occurred in a dominant manner, an inheritance pattern not previously described for immunodeficiency resembling that seen in these half-sisters.

It is possible that these infants had the acquired immune deficiency syndrome (AIDS). Although the mother of the infant in case 1 was not studied immunologically, her death from PCP was probably secondary to AIDS. The mothers of the other three infants were Haitian or intravenous drug abusers, groups at increased risk for AIDS (3). The immunologic features described in the case reports resemble those seen both in adults with AIDS (4) and in a child reported to have developed immunodeficiency following receipt of blood products from a patient with AIDS (5). Case 2 had essentially normal T-cell responses to mitogens in vitro. This finding is atypical for AIDS, but it has been seen in a few adult AIDS cases (6).

Although the etiology of AIDS remains unknown, a series of epidemiologic observations suggests it is caused by an infectious agent (3,5,7-9). If the infants described in the four case reports had AIDS, exposure to the putative "AIDS agent" must have occurred very early. Cases 2-4 were less than 6 months old when they had serious opportunistic infections. Case 1 had oral candidiasis beginning at 3 months of age, although M. avium-intracellulare infection was not documented until 17 months. Transmission of an "AIDS agent" from mother to child, either in utero or shortly after birth, could account for the early onset of immunodeficiency in these infants.

The relationship between the illnesses seen in the reported cases with severe opportunistic infection and the 12 infants without such infections is unclear at present. The immune dysfuction seen in the children and the sociodemographic profiles of the mothers appear similar in both groups. Prospective study of the 12 children is necessary to define the natural history of their illnesses and the possible relationship of their illnesses to AIDS.

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MMWR Weekly January 07, 1983 / 31(52);697-8

Epidemiologic Notes and Reports Immunodeficiency among Female Sexual Partners of Males with Acquired Immune Deficiency Syndrome (AIDS) -- New York

CDC has received reports of two females with cellular immunodeficiency who have been steady sexual partners of males with the acquired immune deficiency syndrome (AIDS).

Case 1: A 37-year-old black female began losing weight and developed malaise in June 1982. In July, she had oral candidiasis and generalized lymphadenopathy and then developed fever, non-productive cough, and diffuse intestitial pulmonary infiltrates. A transbronchial biopsy revealed Pneumocystis carinii pneumonia (PCP). Immunologic studies showed elevated immunoglobulin levels, lymphopenia, and an undetectable number of T-helper cells. She responded to antimicrobial therapy, but 3 months after hospital discharge had lymphadenopathy, oral candidiasis, and persistent depletion of T-helper cells.

The patient had no previous illnesses or therapy associated with immunosuppression. She admitted to moderate alcohol consumption, but denied intravenous (IV) drug abuse. Since 1976, she had lived with and had been the steady sexual partner of a male with a history of IV drug abuse. He developed oral candidiasis in March 1982 and in June had PCP. He had laboratory evidence of immune dysfunction typical of AIDS and died in November 1982.

Case 2: A 23-year-old Hispanic female was well until February 1982 when she developed generalized lymphadenopathy. Immunologic studies showed elevated immunoglobulin levels, lymphopenia, decreased T-helper cell numbers, and a depressed T-helper/T-suppressor cell ratio (0.82). Common infectious causes of lymphadenopathy were excluded by serologic testing. A lymph node biopsy showed lymphoid hyperplasia. The lymphadenopathy has persisted for almost a year; no etiology for it has been found.

The patient had no previous illnesses or therapy associated with immunosuppression and denied IV drug abuse. Since the summer of 1981, her only sexual partner has been a bisexual male who denied IV drug abuse. He developed malaise, weight loss and lymphadenopathy in June 1981 and oral candidiasis and PCP in June 1982. Skin lesions, present for 6 months, were biopsied in June 1982 and diagnosed as Kaposi's sarcoma. He has laboratory evidence of immune dysfunction typical of AIDS and remains alive. Reported by C Harris, MD, C Butkus Small, MD, G Friedland, MD, R Klein, MD, B Moll, PhD, E Emeson, MD, I Spigland, MD, N Steigbigel, MD, Depts of Medicine and Pathology, Montefiore Medical Center, North Central Bronx Hospital, and Albert Einstein College of Medicine, R Reiss, S Friedman, MD, New York City Dept of Health, R Rothenberg, MD, State Epidemiologist, New York State Dept of Health; AIDS Activity, Center for Infectious Diseases,

CDC.

Editorial Note

Editorial Note: Each reported female patient developed immunodeficiency during a close relationship, including repeated sexual contact, with a male who had AIDS. Patient 1 fits the CDC case definition of AIDS used for epidemiologic surveillance (1). Patient 2 does not meet this definition, but her persistent, generalized lymphadenopathy and cellular immunodeficiency suggest a syndrome described among homosexual men (2). The epidemiologic and immunologic features of this "lymphadenopathy syndrome" and the progression of some patients with this syndrome to Kaposi's sarcoma and opportunistic infections suggest it is part of the AIDS spectrum (3,4). Other than their relationships with their male sexual partners, neither patient had any apparent risk factor for AIDS. Both females specifically denied IV drug abuse.

Epidemiologic observations increasingly suggest that AIDS is caused by an infectious agent. The description of a cluster of sexually related AIDS patients among homosexual males in southern California suggested that such an agent could be transmitted sexually or through other intimate contact (5). AIDS has also been reported in both members of a male homosexual couple in Denmark (6). The present report supports the infectious-agent hypothesis and the possibility that transmission of the putative "AIDS agent" may occur among both heterosexual and male homosexual couples.

Since June 1981, CDC has received reports of 43 previously healthy females who have developed PCP or other opportunistic infections typical of AIDS. Of these 43 patients, 13 were reported as neither Haitians nor IV drug abusers. One of these 13 females is described in case 1; another four, including two wives, are reported to be steady sexual partners of male IV drug abusers. Although none of the four male partners has had an overt illness suggesting AIDS, immunologic studies of blood specimens from one of these males have shown abnormalities of lymphoproliferative response (7). Conceivably, these male drug abusers are carriers of an infectious agent that has not made them ill but caused AIDS in their infected female sexual partners.

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March 04, 1983 / 32(8);101-3

Current Trends Prevention of Acquired Immune Deficiency Syndrome (AIDS): Report of Inter-Agency Recommendations

Since June 1981, over 1,200 cases of acquired immune deficiency syndrome (AIDS) have been reported to CDC from 34 states, the District of Columbia, and 15 countries. Reported cases of AIDS include persons with Kaposi's sarcoma who are under age 60 years and/or persons with life-threatening opportunistic infections with no known underlying cause for immune deficiency. Over 450 persons have died from AIDS, and the case-fatality rate exceeds 60% for cases first diagnosed over 1 year previously (1,2). Reports have gradually increased in number. An average of one case per day was reported during 1981, compared with three to four daily in late 1982 and early 1983. Current epidemiologic evidence identifies several groups in the United States at increased risk for developing AIDS (3-7). Most cases have been reported among homosexual men with multiple sexual partners, abusers of intravenous (IV) drugs, and Haitians, especially those who have entered the country within the past few years. However, each group contains many persons who probably have little risk of acquiring AIDS. Recently, 11 cases of unexplained, life-threatening opportunistic infections and cellular immune deficiency have been diagnosed in patients with hemophilia. Available data suggest that the severe disorder of immune regulation underlying AIDS is caused by a transmissible agent.

A national case-control study and an investigation of a cluster of cases among homosexual men in California indicate that AIDS may be sexually transmitted among homosexual or bisexual men (8,9). AIDS cases were recently reported among women who were steady sexual partners of men with AIDS or of men in high-risk groups, suggesting the possibility of heterosexual transmission (10). Recent reports of unexplained cellular immunodeficiencies and opportunistic infections in infants born to mothers from groups at high risk for AIDS have raised concerns about in utero or perinatal transmission of AIDS (11). Very little is known about risk factors for Haitians with AIDS.

The distribution of AIDS cases parallels that of hepatitis B virus infection, which is transmitted sexually and parenterally. Blood products or blood appear responsible for AIDS among hemophilia patients who require clotting factor replacement. The likelihood of blood transmission is supported by the occurrence of AIDS among IV drug abusers. Many drug abusers share contaminated needles, exposing themselves to blood-borne agents, such as hepatitis B virus. Recently, an infant developed severe immune deficiency and an opportunistic infection several months after receiving a transfusion of platelets derived from the blood of a man subsequently found to have AIDS (12). The possibility of acquiring AIDS through blood components or blood is further suggested by several cases in persons with no known risk factors who have received blood products or blood within 3 years of AIDS diagnosis (2). These cases are currently under investigation.

No AIDS cases have been documented among health care or laboratory personnel caring for AIDS patients or processing laboratory specimens. To date, no person-to-person transmission has been

identified other than through intimate contact or blood transfusion.

Several factors indicate that individuals at risk for transmitting AIDS may be difficult to identify. A New York City study showed that a significant proportion of homosexual men who were asymptomatic or who had nonspecific symptoms or signs (such as generalized lymphadenopathy) had altered immune functions demonstrated by in vitro tests (2,13,14). Similar findings have been reported among patients with hemophilia (2,15,16). Although the significance of these immunologic alterations is not yet clear, their occurrence in at least two groups at high risk for AIDS suggests that the pool of persons potentially capable of transmitting an AIDS agent may be considerably larger than the presently known number of AIDS cases. Furthermore, the California cluster investigation and other epidemiologic findings suggest a "latent period" of several months to 2 years between exposure and recognizable clinical illness and imply that transmissibility may precede recognizable illness. Thus, careful histories and physical examinations alone will not identify all persons capable of transmitting AIDS but should be useful in identifying persons with definite AIDS diagnoses or related symptoms, such as generalized lymphadenopathy, unexplained weight loss, and thrush. Since only a small percentage of members of high-risk groups actually has AIDS, a laboratory test is clearly needed to identify those with AIDS or those at highest risk of acquiring AIDS. For the above reasons, persons who may be considered at increased risk of AIDS include those with symptoms and signs suggestive of AIDS; sexual partners of AIDS patients; sexually active homosexual or bisexual men with multiple partners; Haitian entrants to the United States; present or past abusers of IV drugs; patients with hemophilia; and sexual partners of individuals at increased risk for AIDS.

Statements on prevention and control of AIDS have been issued by the National Gay Task Force, the National Hemophilia Foundation, the American Red Cross, the American Association of Blood Banks, the Council of Community Blood Centers, the American Association of Physicians for Human Rights, and others. These groups agree that steps should be implemented to reduce the potential risk of transmitting AIDS through blood products, but differ in the methods proposed to accomplish this goal. Public health agencies, community organizations, and medical organizations and groups share the responsibility to rapidly disseminate information on AIDS and recommended precautions.

Although the cause of AIDS remains unknown, the Public Health Service recommends the following actions:

1. Sexual contact should be avoided with persons known or suspected to have AIDS. Members of high risk groups should be aware that multiple sexual partners increase the probability of developing AIDS.

2. As a temporary measure, members of groups at increased risk for AIDS should refrain from donating plasma and/or blood. This recommendation includes all individuals belonging to such groups, even though many individuals are at little risk of AIDS. Centers collecting plasma and/or blood should inform potential donors of this recommendation. The Food and Drug Administration (FDA) is preparing new recommendations for manufacturers of plasma derivatives and for establishments collecting plasma or blood. This is an interim measure to protect recipients of blood products and blood until specific laboratory tests are available.

3. Studies should be conducted to evaluate screening procedures for their effectiveness in identifying and excluding plasma and blood with a high probability of transmitting AIDS. These procedures should include specific laboratory tests as well as careful histories and

physical examinations.

4. Physicians should adhere strictly to medical indications for transfusions, and autologous blood transfusions are encouraged.

5. Work should continue toward development of safer blood products for use by hemophilia patients. The National Hemophilia Foundation has made specific

recommendations for management of patients with hemophilia (17).

The interim recommendation requesting that high-risk persons refrain from donating plasma and/or blood is especially important for donors whose plasma is recovered from plasmapheresis centers or other sources and pooled to make products that are not inactivated and may transmit infections, such as hepatitis B. The clear intent of this recommendation is to eliminate plasma and blood potentially containing the putative AIDS agent from the supply. Since no specific test is known to detect AIDS at an early stage in a potential donor, the recommendation to discourage donation must encompass all members of groups at increased risk for AIDS, even though it includes many individuals who may be at little risk of transmitting AIDS.

As long as the cause remains unknown, the ability to understand the natural history of AIDS and to undertake preventive measures is somewhat compromised. However, the above recommendations are prudent measures that should reduce the risk of acquiring and transmitting AIDS. Reported by the Centers for Disease Control, the Food and Drug Administration, and the National Institutes of Health.

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Antibodies to a Retrovirus Etiologically Associated with Acquired Immunodeficiency Syndrome (AIDS) in Populations with Increased Incidences of the Syndrome

Evidence implicates a retrovirus as the etiologic agent of acquired immunodeficiency syndrome (AIDS). Two prototype isolates have been described. One was isolated from the lymph node cells of a homosexual man with unexplained generalized lymphadenopathy, a syndrome associated with AIDS, and was termed lymphadenopathy-associated virus (LAV) (1). A morphologically similar T-lymphotropic retrovirus (HTLV-III) was isolated from lymphocytes of 26 (36%) of 72 patients with AIDS and from 18 (86%) of 21 patients with conditions thought to be related to AIDS (2). The isolation of retroviruses antigenically identical to LAV from a blood donor-recipient pair, each of whom developed AIDS, provides further evidence that this virus is the etiologic agent of AIDS and may be transmitted through blood transfusion (3).

Although direct comparative results have not been published, HTLV-III and LAV are likely to be the same virus because: they have the same appearance by electron microscopy; they are both lymphotropic and cytopathic for OKT-4 cells; isolates from American AIDS patients, when compared, were immunologically indistinguishable from LAV (3); serologic tests of a large number of specimens from patients with AIDS or related conditions show similar results when either of the prototype viruses is used as antigen (4); and preliminary results suggest that LAV and HTLV-III are at least highly related based on competitive radioimmunoassay of their core proteins (5).

Three basic serologic procedures are currently described for detection of antibody to HTLV-III/LAV: an enzyme-linked immunosorbent assay (ELISA) to whole disrupted virus (6-8); a radioimmunoprecipitation assay (RIPA) to the presumed major core protein (called p25) of LAV (9); and assay of antibody to major viral antigens by the Western blot technique (10, 11). Sera from several high-risk populations are being tested by these techniques by the National Cancer Institute, the Institut Pasteur, and CDC, with the support of numerous collaborators. The objectives of these investigations are to determine the frequency of exposure to HTLV-III/LAV and to correlate seropositivity with current infection, clinical signs and symptoms, and prognosis.

Preliminary data suggest that serologic evidence of exposure to HTLV-III/LAV may be common in certain populations at increased risk for AIDS. Antibody to HTLV-III was detected by ELISA in sera from six (35%) of 17 American homosexual men without symptoms of AIDS (6). Sera from eight (18%) of 44 homosexual men without lymphadenopathy attending a venereal disease clinic in Paris had antibody detected by ELISA to LAV (7). Antibody prevalence to LAV (RIPA) has increased from 1% (1/100) in 1978 to 25% (12/48) in 1980 and 65% (140/215) in 1984 among samples of sera from homosexual men attending a sexually transmitted diseases clinic in San Francisco (12).

Antibody prevalence among the above men tested in 1984 who had no symptoms or clinical signs of AIDS or related conditions was 55% (69/126) (12). In New York City, where the AIDS cases among intravenous (IV) drug users are concentrated, 87% (75/86) of recent heavy IV drug users without AIDS had antibody to LAV by ELISA, while over 58% (50/86) of the same group had antibody to LAV detected by RIPA (13). In contrast, fewer than 10% of 35 methadone patients from New York City had antibody to LAV detected by RIPA. All of these latter patients had been in treatment at least 3 years with greatly reduced IV drug usage (14). Seventy-two percent (18/25) of asymptomatic persons with hemophilia A in a home-care treatment program demonstrated antibody to LAV antigens utilizing the Western blot technique (11). All had used factor VIII concentrates from 1980 to 1982. Reported by DC Des Jarlais, PhD, New York State Div of Substance Abuse Svcs, M Marmor, PhD, H Cohen, MPH, New York University Medical Center, S Yancovitz, MD, J Garber, Beth Israel Medical Center, S Friedman, PhD, Narcotic and Drug Research, MJ Kreek, MD, A Miescher, MD, E Khuri, MD, Rockefeller University, New York City, SM Friedman, MD, New York City Dept of Health, R Rothenberg, MD, State Epidemiologist, New York State Dept of Health; D Echenberg, MD, P O'Malley, E Braff, MD, San Francisco City/County Health Dept, J Chin, MD, State Epidemiologist, California Dept of Health Svcs; P Burtenol, MD, Hemophilia of Georgia, Atlanta, RK Sikes, DVM, State Epidemiologist, Georgia Dept of Human Resources; Div of Viral Diseases, Div of Host Factors, AIDS Activity, Center for Infectious Diseases, CDC.

Editorial Note

Editorial Note: The high prevalence of antibody to HTLV-III/LAV among these groups and the increasing prevalence among homosexual men in San Francisco add further support to HTLV-III/LAV being the etiologic agent of AIDS. They further demonstrate that exposure to the virus is much more common than AIDS itself among populations with increased incidences of the disease. If AIDS follows the pattern of many other infectious diseases, host response to infection would be expected to range from subclinical to severe. Milder disease states for AIDS have been suspected, since the reported frequency of lymphadenopathy and immunologic abnormalities, conditions associated with AIDS, has also been high in these groups. These data, based on limited samples of high-risk groups, suggest the spectrum of response to infection with HTLV-III/LAV may be wide.

These serologic tests are sufficiently sensitive and specific to be of value in estimating the frequency of infection with HTLV-III/LAV in certain populations and for providing important information about the natural history of the disease in such groups. Less clear are the implications of a positive test result for an individual. For some, the result may be a false positive caused by infection with an antigenically related virus or nonspecific test factors. The determination of the frequency and cause of falsely positive tests is essential for proper interpretation of test results, but remains to be established, particularly in populations, such as blood donors who belong to no known AIDS risk groups, where the prevalence of true infection with HTLV-III/LAV is expected to be very low.

A positive test for most individuals in populations at greater risk of acquiring AIDS will probably mean that the individual has been infected at some time with HTLV-III/LAV. Whether the person is currently infected or immune is not known, based on the serologic test alone--HTLV-III/LAV has been isolated in both the presence and absence of antibody--but the frequency of virus in antibody-positive persons is yet to be determined. For seropositive individuals with mild or no signs of disease, including those in whom the virus can be demonstrated, the prognosis remains uncertain. The incubation period for the life-threatening manifestations of AIDS may range from 1 year to more than 4 years (15).

Carefully planned and executed studies will be required to resolve these issues, and to clarify remaining questions about the natural history of AIDS and risk factors for transmission of the virus.

Until the usefulness of positive and negative serologic tests is fully established, all individuals in populations with increased incidences of AIDS, as well as those outside such groups with positive tests, should comply with the March 1983 Public Health Service recommendations for the prevention of AIDS to minimize the transmission of the syndrome (16). Abstention from IV drug usage and reduction of needle-sharing and other use of contaminated needles by IV drug users should also be effective in preventing transmission of the virus and of AIDS. There remains no evidence of transmission of AIDS through casual contact. Prevention measures should stress that transmission has been only through intimate sexual contact, sharing of contaminated needles, or, less frequently, through transfusion of blood or blood products.

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Current Trends Recommendations for Assisting in the Prevention of Perinatal Transmission of Human T-Lymphotropic Virus Type III/Lymphadenopathy-Associated Virus and Acquired Immunodeficiency Syndrome

The information and recommendations in this document are intended to assist health-care providers and state and local health departments in developing procedures to prevent perinatal transmission of human T-lympho- tropic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV), the virus that causes acquired immunodeficiency syndrome (AIDS).

This document contains recommendations for providing counselling and, when indicated, testing for antibody to HTLV-III/LAV for women who are at increased risk of acquiring the virus and who are either pregnant or may become pregnant. It is important that these women know they are at risk, as well as know and understand their HTLV-III/LAV-antibody status, so they can make informed decisions to help prevent perinatally acquired HTLV-III/LAV.

Through counselling, uninfected women can learn how to avoid becoming infected, and infected women can choose to delay pregnancy until more is known about perinatal transmission of the virus. If already pregnant, infected women can be provided information for managing the pregnancy and caring for the child.

Currently available data indicate that most pediatric HTLV-III/LAV infections and AIDS are acquired perinatally from infected women, but additional studies are needed to better quantify the risk of transmission from an infected pregnant woman to the fetus or newborn.

The recommendations below pertain to women. However, men who are HTLV- III/LAV-antibody positive should also be counselled regarding the risks of sexual and perinatal transmission, so they can refer for counselling and testing their sex partners who may be pregnant or considering pregnancy.

BACKGROUND

Pediatric AIDS Cases due to Perinatal Transmission. As of December 1, 1985, 217 (1%) of the 15,172 AIDS cases reported to CDC occurred among children under 13 years of age. Sixty percent of these children are known to have died. These 217 cases represent only the more severe manifestations

of HTLV-III/LAV infection. Less severe manifestations, often described as AIDS- related complex (ARC), are not reported to CDC, so the number of children with clinically significant illness attributable to HTLV-III/LAV infection is greater than the reported cases of pediatric AIDS. In addition, a number of infected children are probably asymptomatic.

Of the 217 reported pediatric AIDS patients, 165 (76%) have as their only known risk factor a mother belonging to a group with increased prevalence of HTLV-III/LAV infection. An additional 18% of the pediatric cases are attributable to transfusions of blood or blood products, while risk factor information is missing or incomplete on the remaining 6%. Of the 217 children with AIDS, 48% had mothers who were intravenous (IV) drug abusers; 17% had mothers who were born in Haiti; and 10% had mothers who were sex partners of either IV drug abusers or bisexual men.

Of the patients with perinatally acquired AIDS, 45% resided in New York City, while Florida and New Jersey accounted for an additional 32%.

Mechanisms of Perinatal Transmission. It is believed that HTLV-III/LAV is transmitted from infected women to their fetuses or offspring during pregnancy, during labor and delivery, or perhaps shortly after birth. Trans- mission of the virus during pregnancy or labor and delivery is demonstrated by two reported AIDS cases occurring in children who had no contact with their infected mothers after birth. One was delivered by Cesarean section (1,2).

Transmission of the virus after birth has been implicated in one case of HTLV-III/LAV infection in a child born to a mother reported to have acquired the infection from a postpartum blood transfusion. Since she breastfed the child for 6 weeks, the authors suggested breastfeeding as the possible mode of transmission (3). Recently, HTLV-III/LAV has been isolated from the breast milk of infected women (4).

Risk of Perinatal Transmission from Infected Mothers. The rate of perinatal transmission of HTLV-III/LAV from infected pregnant women is unknown; however, available data suggest a high rate. In one study of 20 infants born to infected mothers who had already delivered one infant with AIDS, 13 (65%) had serologic and/or clinical evidence of infection with HTLV- III/LAV several months after birth (5,6). Since these women were selected on the basis of having previously transmitted HTLV-III/LAV perinatally, this study may overestimate the average risk of transmission for all infected pregnant women.

Perinatal transmission from an infected mother to her newborn is not inevitable. Of three children born to women who became infected with HTLV- III/LAV by artificial insemination from an infected donor, all were in good health and negative for antibody to the virus more than 1 year after birth (7). Another child, born to a woman who was already pregnant at the time of AIDS diagnosis and was demonstrated to be viremic, was seronegative, culture negative, and healthy at birth and at 4 months of age (8). In a retrospective study evaluating nine children under 5 years of age whose mothers were later diagnosed with AIDS, two (22%) had antibody to HTLV-III/LAV (9). The infection status of these women during pregnancy was unknown.

In these studies, the rate of transmission ranged from 0% (0/3) to 65% (13/20). Additional studies are needed to better define the rate of trans- mission and variables associated with it.

Risk of Illness among Infected Pregnant Women. Pregnancy is associated with suppression of cell-mediated immunity and increased susceptibility to some infections (10). The T-helper to T-

suppressor ratio is decreased during normal pregnancy, being lowest in the third trimester, and returns to normal approximately 3 months postpartum (10). It is not known whether pregnancy increases an infected woman's risk of developing AIDS or ARC, but one study suggests it does (6). Fifteen infected women who were well at time of delivery were followed an average of 30 months after the births of their children. Five (33%) subsequently developed AIDS; seven (47%) developed AIDS-related conditions; and only three (20%) remained asymptomatic. These results may not apply to all infected pregnant women, but they do suggest an increased likelihood of developing disease when an HTLV-III/LAV infection occurs in association with pregnancy.

Prevalence of HTLV-III/LAV Infection. Counselling and testing for antibody to HTLV-III/LAV, when indicated, to reduce perinatal transmission of AIDS will be most beneficial in populations of women with increased prevalence of the virus (Table 1). These include: women who have used drugs intravenously for nonmedical purposes; women who were born in countries where heterosexual transmission is thought to play a major role (11,12); women who have engaged in prostitution; and women who are or have been sex partners of men who abuse IV drugs, are bisexual, have hemophilia, were born in countries where heterosexual transmission is thought to play a major role (11,12), or have evidence of HTLV-III/LAV infection.

The prevalence of antibody to HTLV-III/LAV in U.S. populations of men and women ranges from less than 0.01% in female blood donors to as high as 74% in men with hemophilia (13-15). Among heterosexual IV drug abusers, the prevalence of HTLV-III/LAV infection ranges from 2% to 59% in various geographic areas (16,17). Seroprevalence among the heterosexual partners of persons at increased risk for AIDS varies from 10% in female partners of asymptomatic, seropositive hemophilia patients to 71% in the female partners of men with AIDS or ARC (18-20). Among prostitutes, the HTLV-III/LAV antibody prevalence varies from 5% to 40%, depending on geographic area, with most of the women with positive tests relating histories of IV drug abuse (21). Among female blood donors in Atlanta, Georgia, who denied belonging to high-risk groups, 0.01% had repeatedly reactive enzyme-linked immunosorbent assays (ELISAs) followed by reactive Western blot tests (15).

Commercially available tests to detect antibody to HTLV-III/LAV are ELISAs using antigens derived from whole disrupted HTLV-III/LAV. When the ELISA is reactive on initial testing, it is standard procedure to repeat the test on the same specimen. Repeatedly reactive tests are highly sensitive and specific for antibody to HTLV-III/LAV. However, when the ELISA is used to screen populations in which the prevalence of infection is very low (such as blood donors or women not in high-risk groups), the proportion of repeatedly reactive results that are falsely positive will be higher. For that reason, an additional test, such as a Western blot, is recommended following repeatedly reactive ELISA results, especially in low-prevalence populations. In populations with high prevalence of infection (e.g. homosexual men or IV drug abusers), most repeatedly reactive ELISAs are reactive by Western blot or another test. For example, among 109 IV drug abusers whose sera were repeatedly reactive by ELISA, over 85% were reactive by Western blot (22). In contrast, in a low-prevalence population of 69 female blood donors whose sera were repeatedly reactive by ELISA, only 5% were reactive by Western blot (15).

Due to the seriousness of the implications of HTLV-III/LAV-antibody reactivity, it is recommended that repeatedly reactive ELISAs be followed by an additional test, such as the Western blot. Women with sera repeatedly reactive by ELISA and reactive by western blot should have a thorough medical evaluation. HTLV-III/LAV has been isolated from a single specimen in 67%-95% of persons with specific antibody (23,24). Because infection has been demon- strated in asymptomatic persons, the

presence of specific antibody should be considered presumptive evidence of current infection and infectiousness.

RECOMMENDATIONS

Women Who Should be Offered Counselling and Testing. Counselling services and testing for antibody to HTLV-III/LAV should be offered to pregnant women and women who may become pregnant in the following groups: (1) those who have evidence of HTLV-III/LAV infection; (2) those who have used drugs intra- venously for nonmedical purposes; (3) those who were born in countries where heterosexual transmission is thought to play a major role (11,12); (4) those who have engaged in prostitution; (5) those who are or have been sex partners of: IV drug abusers, bisexual men, men with hemophilia, men who were born in countries where heterosexual transmission is thought to play a major role (11,12), or men who otherwise have evidence of HTLV-III/LAV infection. If data become available to show that HTLV-III/LAV-antibody prevalence is increased in other groups or settings, counselling and testing programs should be extended to include them. Routine counselling and testing of women who are not included in the above-mentioned groups is not recommended due to low prevalence of infection and concern about interpretation of test results in a low-prevalence population. However if a women requests it, the service should be provided in accordance with these recommendations.

Settings for Offering Counselling and Testing. Counselling and testing for antibody to HTLV-III/LAV to prevent perinatal transmission is recommended in the setting of any medical service in which women at increased risk are commonly encountered. These include services for treating IV drug abuse (i.e., detoxification and methadone maintenance), comprehensive hemophilia treatment centers, sexually transmitted disease clinics, and clinics that serve female prostitutes. In addition, services related to reproduction, such as family planning and infertility services, gynecologic, premarital, or preconceptual examinations, and prenatal and obstetric services should also consider offering counselling and testing if high-risk women are seen at these facilities. Testing for antibody to HTLV-III/LAV should be performed with the woman's consent after counselling is provided regarding risk factors for infection, the interpretation of test results, the risks of transmission, and the possible increased likelihood of disease among women infected with HTLV-III/LAV in association with pregnancy. The counselling and testing must be conducted in an environment in which confidentiality can be assured. In settings where confidential counselling and testing cannot be assured, infor- mation should be provided and referrals made to appropriate facilities.

Frequency of Testing. Detectable antibodies to HTLV-III/LAV may not develop until 2-4 months after exposure. This, and whether the woman is continuously exposed, should be taken into account when considering the need for, and frequency of, repeat testing. High-risk women should be offered counselling and testing before they become pregnant. During pregnancy, counselling and testing should be offered as soon as the woman is known to be pregnant. If the initial test is negative, repeat testing may be indicated near delivery to aid in the clinical management of the pregnant woman and newborn. If this final test is negative and the mother's risk of exposure no longer exists, she may safely consider breastfeeding the child, and manage- ment of the child need not include the same concerns that would be appro- priate if the woman had had a positive test or if she were at high risk and had not been tested at all.

Counselling Women with Positive Results. Women with virologic or sero- logic evidence of HTLV-III/LAV infection should be counselled regarding their own risk of AIDS and the risk of perinatal and sexual transmission of HTLV- III/LAV. Infected women should be counselled to refer their sex

partners for counselling and testing. If the partners of these women are not infected, both members of the couple should be counselled on how they may modify their sexual practices to reduce the risk of HTLV-III/LAV transmission to the unin- fected partner. In addition, the couple should be told not to donate blood, organs, or sperm and should be discouraged from using IV drugs and advised against sharing needles and syringes. When seeking medical or dental care for intercurrent illness, they should inform those responsible for their care of their positive antibody status so appropriate evaluation can be undertaken. Recommendations for providing information and advice to individuals infected with HTLV-III/LAV have been published (25).

Infected women should be advised to consider delaying pregnancy until more is known about perinatal transmission of the virus. Pregnant infected women may require additional medical and social support services due to an enhanced risk of opportunistic infections and psychosocial difficulties during and after pregnancy. Obstetric-care providers should be alert to signs and symptoms of HTLV-III/LAV and related opportunistic infections in these pregnant women and to the need for specialized medical care.

HTLV-III/LAV-infected women should be advised against breastfeeding to avoid postnatal transmission to a child who may not yet be infected. The child should receive follow-up pediatric evaluations to determine whether he/she has HTLV-III/LAV infection, and to diagnose and treat promptly any diseases that may be secondary to HTLV-III/LAV infection. Recommendations for educating and providing foster care for infected children have been published (26).

Counselling Women with Negative Test Results. A negative ELISA for HTLV- III/LAV antibody in women who have no clinical or laboratory evidence of HTLV-III/LAV infection is evidence that they have probably not been infected. However, uninfected women who have sex partners with evidence of HTLV-III/LAV infection or with an increased risk of becoming infected should be informed that sexual intercourse increases their risk of infection. These women should be informed of the risks associated with pregnancy if they become infected and advised to consider delaying pregnancy until more is known about peri- natal transmission of the virus or until they are no longer considered to be at risk for acquiring the virus. In addition to preventing pregnancy, the consistent and proper use of condoms can offer some protection against HTLV- III/LAV infection.

High-risk women, even if seronegative, should be told not to donate blood or organs. To decrease their risk of becoming infected, IV drug abusers should be encouraged to seek treatment for their drug abuse. Persons coun- selling IV drug abusers should know that IV drug abuse is often strongly ingrained and compulsive. Despite educational efforts and encouragement for treatment, some addicts will continue to abuse drugs or relapse after treatment. If drug abuse continues, they should be advised not to share needles or syringes and to use only sterile equipment.

Additional Considerations. These recommendations will be revised as additional information becomes available. It is recognized that provision of the recommended professional counselling, HTLV-III/LAV-antibody testing and associated specialized medical services will take time to implement and may stress available resources, particularly in public facilities, which are most greatly affected. Health-care providers, social-service personnel, and others involved in educating and caring for HTLV-III/LAV-infected persons should be aware of the potential for social isolation and should be sensitive to the need for confidentiality. They should be familiar with federal and state laws, regulations, and policies that protect the confidentiality of clinical data and test results. Each institution should assure that specific mechanisms are in place to protect the confidentiality of all records and to prevent the misuse of information. Anonymous testing would not be appropriate if it

prevents adequate counselling and medical follow-up evaluation.

Hospital precautions for managing infected women and infants should be patterned after those for caring for patients with HTLV-III/LAV infection (27,28). Additional recommendations will follow.

DEVELOPMENT OF THESE RECOMMENDATIONS

The information and recommendations contained in this document were developed and compiled by CDC and the U.S. Public Health Service in consul- tation with individuals representing: the Conference of State and Territorial Epidemiologists, the Association of State and Territorial Health Officials, the American Public Health Association, the United States Conference of Local Health Officers, the American Medical Association, the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, the Planned Parenthood Federation of America, the American Venereal Disease Association, the Division of Maternal and Child Health of the Health Resources and Services Administration, the National Institute on Drug Abuse of the Alcohol, Drug Abuse, and Mental Health Administration, the National Hemophilia Foundation, the Haitian Medical Association, the American Bar Foundation, and the Kennedy Institute of Ethics at Georgetown University. The consultants also included representatives of the departments of health of the areas with the largest number of perinatally transmitted pediatric AIDS cases: New York City, Florida, and New Jersey. These recommendations may not reflect the views of all individual consultants or the organizations they represented.

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Perspectives in Disease Prevention and Health Promotion Public Health Service Guidelines for Counseling and Antibody Testing to Prevent HIV Infection and AIDS

These guidelines are the outgrowth of the 1986 recommendations published in the MMWR (1); the report on the February 24-25, 1987, Conference on Counseling and Testing (2); and a series of meetings with representatives from the Association of State and Territorial Health Officials, the Association of State and Territorial Public Health Laboratory Directors, the Council of State and Territorial Epidemiologists, the National Association of County Health Officials, the United States Conference of Local Health Officers, and the National Association of State Alcohol and Drug Abuse Directors.

Human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS) and related clinical manifestations, has been shown to be spread by sexual contact; by parenteral exposure to blood (most often through intravenous (IV) drug abuse) and, rarely, by other exposures to blood; and from an infected woman to her fetus or infant.

Persons exposed to HIV usually develop detectable levels of antibody against the virus within 6-12 weeks of infection. The presence of antibody indicates current infection, though many infected persons may have minimal or no clinical evidence of disease for years. Counseling and testing persons who are infected or at risk for acquiring HIV infection is an important component of prevention strategy (1). Most of the estimated 1.0 to 1.5 million infected persons in the United States are unaware that they are infected with HIV. The primary public health purposes of counseling and testing are to help uninfected individuals initiate and sustain behavioral changes that reduce their risk of becoming infected and to assist infected individuals in avoiding infecting others.

Along with the potential personal, medical, and public health benefits of testing for HIV antibody, public health agencies must be concerned about actions that will discourage the use of counseling and testing facilities, most notably the unauthorized disclosure of personal information and the possibility of inappropriate discrimination.

Priorities for public health counseling and testing should be based upon providing ready access to persons who are most likely to be infected or who practice high-risk behaviors, thereby helping to reduce further spread of infection. There are other considerations for determining testing priorities, including the likely effectiveness of preventing the spread of infection among persons who would not otherwise realize that they are at risk. Knowledge of the prevalence of HIV infection in different populations is useful in determining the most efficient and effective locations providing such services. For example, programs that offer counseling and testing to homosexual men, IV-drug

abusers, persons with hemophilia, sexual and/or needle-sharing partners of these persons, and patients of sexually transmitted disease clinics may be most effective since persons in these groups are at high risk for infection. After counseling and testing are effectively implemented in settings of high and moderate prevalence, consideration should be given to establishing programs in settings of lower prevalence. Interpretation of HIV-Antibody Test Results

A test for HIV antibody is considered positive when a sequence of tests, starting with a repeatedly reactive enzyme immunoassay (EIA) and including an additional, more specific assay, such as a Western blot, are consistently reactive.

The sensitivity of the currently licensed EIA tests is 99% or greater when performed under optimal laboratory conditions. Given this performance, the probability of a false-negative test result is remote, except during the first weeks after infection, before antibody is detectable.

The specificity of the currently licensed EIA tests is approximately 99% when repeatedly reactive tests are considered. Repeat testing of specimens initially reactive by EIA is required to reduce the likelihood of false-positive test results due to laboratory error. To further increase the specificity of the testing process, laboratories must use a supplemental test--most often the Western blot test--to validate repeatedly reactive EIA results. The sensitivity of the licensed Western blot test is comparable to that of the EIA, and it is highly specific when strict criteria are used for interpretation. Under ideal circumstances, the probability that a testing sequence will be falsely positive in a population with a low rate of infection ranges from less than 1 in 100,000 (Minnesota Department of Health, unpublished data) to an estimated 5 in 100,000 (3,4). Laboratories using different Western blot reagents or other tests or using less stringent interpretive criteria may experience higher rates of false-positive results.

Laboratories should carefully guard against human errors, which are likely to be the most common source of false-positive test results. All laboratories should anticipate the need for assuring quality performance of tests for HIV antibody by training personnel, establishing quality controls, and participating in performance evaluation systems. Health department laboratories should facilitate the quality assurance of the performance of laboratories in their jurisdiction. Guidelines for Counseling and Testing for HIV Antibody

These guidelines are based on public health considerations for HIV testing, including the principles of counseling before and after testing, confidentiality of personal information, and the understanding that a person may decline to be tested without being denied health care or other services, except where testing is required by law (5). Counseling before testing may not be practical when screening for HIV antibody is required. This is true for donors of blood, organs, and tissue; prisoners; and immigrants for whom testing is a Federal requirement as well as for persons admitted to state correctional institutions in states that require testing. When there is no counseling before testing, persons should be informed that testing for HIV antibody will be performed, that individual results will be kept confidential to the extent permitted by law, and that appropriate counseling will be offered. Individual counseling of those who are either HIV-antibody positive or at continuing risk for HIV infection is critical for reducing further transmission and for ensuring timely medical care. Specific recommendations follow:

1. Persons who may have sexually transmitted disease. All persons seeking treatment for a sexually transmitted disease, in all health-care settings including the offices of private physicians, should be routinely * counseled and tested for HIV antibody.

2. IV-drug abusers. All persons seeking treatment for IV-drug abuse or having a history of IV-drug abuse should be routinely counseled and tested for HIV antibody. Medical professionals in all health-care settings, including prison clinics, should seek a history of IV-drug abuse from patients and should be aware of its implications for HIV infection. In addition, state and local health policy makers should address the following issues:

Treatment programs for IV-drug abusers should be sufficiently available to allow persons seeking assistance to enter promptly and be encouraged to alter the behavior that places them and others at risk for HIV infection. Outreach programs for IV-drug abusers should be undertaken to increase their knowledge of AIDS and of ways to prevent HIV infection, to encourage them to obtain counseling and testing for HIV antibody, and to persuade them to be treated for substance abuse. 3. Persons who consider themselves at risk. All persons who

consider themselves at risk for HIV infection should be counseled and offered testing for HIV antibody. 4. Women of childbearing age. All women of childbearing age

with identifiable risks for HIV infection should be routinely counseled and tested for HIV antibody, regardless of the health-care setting. Each encounter between a health-care provider and a woman at risk and/or her sexual partners is an opportunity to reach them with information and education about AIDS and prevention of HIV infection. Women are at risk for HIV infection if they:

Have used IV drugs. Have engaged in prostitution. Have had sexual partners who are infected or are at risk for infection because they are bisexual or are IV-drug abusers or hemophiliacs. Are living in communities or were born in countries where there is a known or suspected high prevalence of infection among women. Received a transfusion before blood was being screened for HIV antibody but after HIV infection occurred in the United States (e.g., between 1978 and 1985). Educating and testing these women before they become pregnant allows them to avoid pregnancy and subsequent intrauterine perinatal infection of their infants (30%-50% of the infants born to HIV-infected women will also be infected). All pregnant women at risk for HIV infection should be routinely counseled and tested for HIV antibody. Identifying pregnant women with HIV infection as early in pregnancy as possible is important for ensuring appropriate medical care for these women; for planning medical care for their infants; and for providing counseling on family planning, future pregnancies, and the risk of sexual transmission of HIV to others.

All women who seek family planning services and who are at risk for HIV infection should be routinely counseled about AIDS and HIV infection and tested for HIV antibody. Decisions about the need for counseling and testing programs in a community should be based on the best available estimates of the prevalence of HIV infection and the demographic variables of infection. 5. Persons planning marriage. All persons considering marriage

should be given information about AIDS, HIV infection, and the availability of counseling and testing for HIV antibody. Decisions about instituting routine or mandatory premarital testing for HIV antibody should take into account the prevalence of HIV infection in the area and/or population group as well as other factors and should be based upon the likely cost-effectiveness of such testing in preventing further spread of infection. Premarital testing in an area with a prevalence of HIV infection as low as 0.1% may be justified if reaching an infected person through testing can prevent subsequent transmission to the spouse or prevent pregnancy in a woman who is infected. 6. Persons undergoing medical evaluation or treatment. Testing

for HIV antibody is a useful diagnostic tool for evaluating patients with selected clinical signs and symptoms such as generalized lymphadenopathy; unexplained dementia; chronic, unexplained fever or diarrhea; unexplained weight loss; or diseases such as tuberculosis as well as sexually transmitted diseases, generalized herpes, and chronic candidiasis. Since persons infected with both HIV and the tubercle bacillus are at high risk for severe clinical tuberculosis, all patients with tuberculosis should be routinely counseled and tested for HIV antibody (6). Guidelines for managing patients with both HIV and tuberculous infection have been published (7).

The risk of HIV infection from transfusions of blood or blood components from 1978-1985 was greatest for persons receiving large numbers of units of blood collected from areas with high incidences of AIDS. Persons who have this increased risk should be counseled about the potential risk of HIV infection and should be offered antibody testing (8). 7. Persons admitted to hospitals. Hospitals, in conjunction

with state and local health departments, should periodically determine the prevalence of HIV infections in the age groups at highest risk for infection. Consideration should be given to routine testing in those age groups deemed to have a high prevalence of HIV infection. 8. Persons in correctional systems. Correctional systems should

study the best means of implementing programs for counseling inmates about HIV infection and for testing them for such infection at admission and discharge from the system. In particular, they should examine the usefulness of these programs in preventing further transmission of HIV infection and the impact of the testing programs on both the inmates and the correctional system (9). Federal prisons have been instructed to test all prisoners when they enter and leave the prison system. 9. Prostitutes. Male and female prostitutes should be counseled

and tested and made aware of the risks of HIV infection to themselves and others. Particularly prostitutes who are HIV-antibody positive should be instructed to discontinue the practice of prostitution. Local or state jurisdictions should adopt procedures to assure that these instructions are followed. Partner Notification/Contact Tracing

Sexual partners and those who share needles with HIV-infected persons are at risk for HIV infection and should be routinely counseled and tested for HIV antibody. Persons who are HIV-antibody positive should be instructed in how to notify their partners and to refer them for counseling and testing. If they are unwilling to notify their partners or if it cannot be assured that their partners will seek counseling, physicians or health department personnel should use confidential procedures to assure that the partners are notified.

Confidentiality and Antidiscrimination Considerations

The ability of health departments, hospitals, and other health-care providers and institutions to assure confidentiality of patient information and the public's confidence in that ability are crucial to efforts to increase the number of persons being counseled and tested for HIV infection. Moreover, to assure broad participation in the counseling and testing programs, it is of equal or greater importance that the public perceive that persons found to be positive will not be subject to inappropriate discrimination.

Every reasonable effort should be made to improve confidentiality of test results. The confidentiality

of related records can be improved by a careful review of actual record-keeping practices and by assessing the degree to which these records can be protected under applicable state laws. State laws should be examined and strengthened when found necessary. Because of the wide scope of "need-to-know" situations, because of the possibility of inappropriate disclosures, and because of established authorization procedures for releasing records, it is recognized that there is no perfect solution to confidentiality problems in all situations. Whether disclosures of HIV- testing information are deliberate, inadvertent, or simply unavoidable, public health policy needs to carefully consider ways to reduce the harmful impact of such disclosures.

Public health prevention policy to reduce the transmission of HIV infection can be furthered by an expanded program of counseling and testing for HIV antibody, but the extent to which these programs are successful depends on the level of participation. Persons are more likely to participate in counseling and testing programs if they believe that they will not experience negative consequences in areas such as employment, school admission, housing, and medical services should they test positive. There is no known medical reason to avoid an infected person in these and ordinary social situations since the cumulative evidence is strong that HIV infection is not spread through casual contact. It is essential to the success of counseling and testing programs that persons who are tested for HIV are not subjected to inappropriate discrimination.

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*"Routine counseling and testing" is defined as a policy to provide these services to all clients after informing them that testing will be done. Except where testing is required by law, individuals have the right to decline to be tested without being denied health care or other services.

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Recommendations for Preventing Transmission of Human Immunodeficiency Virus and Hepatitis B Virus to Patients During Exposure-Prone Invasive Procedures

This document has been developed by the Centers for Disease Control (CDC) to update recommendations for prevention of transmission of human immunodeficiency virus (HIV) and hepatitis B virus (HBV) in the health-care setting. Current data suggest that the risk for such transmission from a health-care worker (HCW) to a patient during an invasive procedure is small; a precise assessment of the risk is not yet available. This document contains recommendations to provide guidance for prevention of HIV and HBV transmission during those invasive procedures that are considered exposure-prone. INTRODUCTION

Recommendations have been made by the Centers for Disease Control (CDC) for the prevention of transmission of the human immunodeficiency virus (HIV) and the hepatitis B virus (HBV) in health-care settings (1-6). These recommendations emphasize adherence to universal precautions that require that blood and other specified body fluids of all patients be handled as if they contain blood-borne pathogens (1,2).

Previous guidelines contained precautions to be used during invasive procedures (defined in Appendix) and recommendations for the management of HIV- and HBV-infected health-care workers (HCWs) (1). These guidelines did not include specific recommendations on testing HCWs for HIV or HBV infection, and they did not provide guidance on which invasive procedures may represent increased risk to the patient.

The recommendations outlined in this document are based on the following considerations:

- Infected HCWs who adhere to universal precautions and who

do not perform invasive procedures pose no risk for transmitting HIV or HBV to patients.

- Infected HCWs who adhere to universal precautions and who

perform certain exposure-prone procedures (see page 4) pose a small risk for transmitting HBV to patients.

- HIV is transmitted much less readily than HBV. In the interim, until further data are available, additional

precautions are prudent to prevent HIV and HBV transmission during procedures that have been linked to HCW-to-patient HBV transmission or that are considered exposure-prone.

BACKGROUND Infection-Control Practices

Previous recommendations have specified that infection-control programs should incorporate principles of universal precautions (i.e., appropriate use of hand washing, protective barriers, and care in the use and disposal of needles and other sharp instruments) and should maintain these precautions rigorously in all health-care settings (1,2,5). Proper application of these principles will assist in minimizing the risk of transmission of HIV or HBV from patient to HCW, HCW to patient, or patient to patient.

As part of standard infection-control practice, instruments and other reusable equipment used in performing invasive procedures should be appropriately disinfected and sterilized as follows (7):

- Equipment and devices that enter the patient's vascular

system or other normally sterile areas of the body should be sterilized before being used for each patient.

- Equipment and devices that touch intact mucous membranes

but do not penetrate the patient's body surfaces should be sterilized when possible or undergo high-level disinfection if they cannot be sterilized before being used for each patient.

- Equipment and devices that do not touch the patient or

that only touch intact skin of the patient need only be cleaned with a detergent or as indicated by the manufacturer.

Compliance with universal precautions and recommendations for disinfection and sterilization of medical devices should be scrupulously monitored in all health-care settings (1, 7, 8). Training of HCWs in proper infection-control technique should begin in professional and vocational schools and continue as an ongoing process. Institutions should provide all HCWs with appropriate inservice education regarding infection control and safety and should establish procedures for monitoring compliance with infection-control policies.

All HCWs who might be exposed to blood in an occupational setting should receive hepatitis B vaccine, preferably during their period of professional training and before any occupational exposures could occur (8, 9).

Transmission of HBV During Invasive Procedures

Since the introduction of serologic testing for HBV infection in the early 1970s, there have been published reports of 20 clusters in which a total of over 300 patients were infected with HBV in association with treatment by an HBV-infected HCW. In 12 of these clusters, the implicated HCW did not routinely wear gloves; several HCWs also had skin lesions that may have facilitated HBV transmission (10-22). These 12 clusters included nine linked to dentists or oral surgeons and one cluster each linked to a general practitioner, an inhalation therapist, and a cardiopulmonary-bypass-

pump technician. The clusters associated with the inhalation therapist and the cardiopulmonary-bypass-pump technician--and some of the other 10 clusters--could possibly have been prevented if current recommendations on universal precautions, including glove use, had been in effect. In the remaining eight clusters, transmission occurred despite glove use by the HCWs; five clusters were linked to obstetricians or gynecologists, and three were linked to cardiovascular surgeons (6, 22-28). In addition, recent unpublished reports strongly suggest HBV transmission from three surgeons to patients in 1989 and 1990 during colorectal (CDC, unpublished data), abdominal, and cardiothoracic surgery (29).

Seven of the HCWs who were linked to published clusters in the United States were allowed to perform invasive procedures following modification of invasive techniques (e.g., double gloving and restriction of certain high-risk procedures) (6,11- 13,15,16, 24). For five HCWs, no further transmission to patients was observed. In two instances involving an obstetrician/gynecologist and an oral surgeon, HBV was transmitted to patients after techniques were modified (6, 12).

Review of the 20 published studies indicates that a combination of risk factors accounted for transmission of HBV from HCWs to patients. Of the HCWs whose hepatitis B e antigen (HBeAg) status was determined (17 of 20), all were HBeAg positive. The presence of HBeAg in serum is associated with higher levels of circulating virus and therefore with greater infectivity of hepatitis-B-surface-antigen (HBsAg)-positive individuals; the risk of HBV transmission to an HCW after a percutaneous exposure to HBeAg-positive blood is approximately 30% (30-32). In addition, each report indicated that the potential existed for contamination of surgical wounds or traumatized tissue, either from a major break in standard infection-control practices (e.g., not wearing gloves during invasive procedures) or from unintentional injury to the infected HCW during invasive procedures (e.g., needle sticks incurred while manipulating needles without being able to see them during suturing).

Most reported clusters in the United States occurred before awareness increased of the risks of transmission of blood-borne pathogens in health-care settings and before emphasis was placed on the use of universal precautions and hepatitis B vaccine among HCWs. The limited number of reports of HBV transmission from HCWs to patients in recent years may reflect the adoption of universal precautions and increased use of HBV vaccine. However, the limited number of recent reports does not preclude the occurrence of undetected or unreported small clusters or individual instances of transmission; routine use of gloves does not prevent most injuries caused by sharp instruments and does not eliminate the potential for exposure of a patient to an HCW's blood and transmission of HBV (6, 22-29).

Transmission of HIV During Invasive Procedures

The risk of HIV transmission to an HCW after percutaneous exposure to HIV-infected blood is considerably lower than the risk of HBV transmission after percutaneous exposure to HBeAg-positive blood (0.3% versus approximately 30%) (33-35). Thus, the risk of transmission of HIV from an infected HCW to a patient during an invasive procedure is likely to be proportionately lower than the risk of HBV transmission from an HBeAg-positive HCW to a patient during the same procedure. As with HBV, the relative infectivity of HIV probably varies among individuals and over time for a single individual. Unlike HBV infection, however, there is currently no readily available laboratory test for increased HIV infectivity.

Investigation of a cluster of HIV infections among patients in the practice of one dentist with

acquired immunodeficiency syndrome (AIDS) strongly suggested that HIV was transmitted to five of the approximately 850 patients evaluated through June 1991 (36-38). The investigation indicates that HIV transmission occurred during dental care, although the precise mechanisms of transmission have not been determined. In two other studies, when patients cared for by a general surgeon and a surgical resident who had AIDS were tested, all patients tested, 75 and 62, respectively, were negative for HIV infection (39, 40). In a fourth study, 143 patients who had been treated by a dental student with HIV infection and were later tested were all negative for HIV infection (41). In another investigation, HIV antibody testing was offered to all patients whose surgical procedures had been performed by a general surgeon within 7 years before the surgeon's diagnosis of AIDS; the date at which the surgeon became infected with HIV is unknown (42). Of 1,340 surgical patients contacted, 616 (46%) were tested for HIV. One patient, a known intravenous drug user, was HIV positive when tested but may already have been infected at the time of surgery. HIV test results for the 615 other surgical patients were negative (95% confidence interval for risk of transmission per operation=0.0%-0.5%).

The limited number of participants and the differences in procedures associated with these five investigations limit the ability to generalize from them and to define precisely the risk of HIV transmission from HIV-infected HCWs to patients. A precise estimate of the risk of HIV transmission from infected HCWs to patients can be determined only after careful evaluation of a substantially larger number of patients whose exposure-prone procedures have been performed by HIV-infected HCWs.

Exposure-Prone Procedures

Despite adherence to the principles of universal precautions, certain invasive surgical and dental procedures have been implicated in the transmission of HBV from infected HCWs to patients, and should be considered exposure-prone. Reported examples include certain oral, cardiothoracic, colorectal (CDC, unpublished data), and obstetric/gynecologic procedures (6, 12, 22-29).

Certain other invasive procedures should also be considered exposure-prone. In a prospective study CDC conducted in four hospitals, one or more percutaneous injuries occurred among surgical personnel during 96 (6.9%) of 1,382 operative procedures on the general surgery, gynecology, orthopedic, cardiac, and trauma services (43). Percutaneous exposure of the patient to the HCW's blood may have occurred when the sharp object causing the injury recontacted the patient's open wound in 28 (32%) of the 88 observed injuries to surgeons (range among surgical specialties=8%-57%; range among hospitals=24%-42%). Characteristics of exposure-prone procedures include digital palpation of a needle tip in a body cavity or the simultaneous presence of the HCW's fingers and a needle or other sharp instrument or object in a poorly visualized or highly confined anatomic site. Performance of exposure-prone procedures presents a recognized risk of percutaneous injury to the HCW, and--if such an injury occurs--the HCW's blood is likely to contact the patient's body cavity, subcutaneous tissues, and/or mucous membranes.

Experience with HBV indicates that invasive procedures that do not have the above characteristics would be expected to pose substantially lower risk, if any, of transmission of HIV and other blood-borne pathogens from an infected HCW to patients. RECOMMENDATIONS

Investigations of HIV and HBV transmission from HCWs to patients indicate that, when HCWs adhere to recommended infection-control procedures, the risk of transmitting HBV from an infected HCW to a patient is small, and the risk of transmitting HIV is likely to be even smaller. However, the likelihood of exposure of the patient to an HCW's blood is greater for certain procedures designated

as exposure-prone. To minimize the risk of HIV or HBV transmission, the following measures are recommended:

--All HCWs should adhere to universal precautions, including the appropriate use of hand washing, protective barriers, and care in the use and disposal of needles and other sharp instruments. HCWs who have exudative lesions or weeping dermatitis should refrain from all direct patient care and from handling patient-care equipment and devices used in performing invasive procedures until the condition resolves. HCWs should also comply with current guidelines for disinfection and sterilization of reusable devices used in invasive procedures.

--Currently available data provide no basis for recommendations to restrict the practice of HCWs infected with HIV or HBV who perform invasive procedures not identified as exposure-prone, provided the infected HCWs practice recommended surgical or dental technique and comply with universal precautions and current recommendations for sterilization/disinfection.

--Exposure-prone procedures should be identified by medical/surgical/dental organizations and institutions at which the procedures are performed.

--HCWs who perform exposure-prone procedures should know their HIV antibody status. HCWs who perform exposure-prone procedures and who do not have serologic evidence of immunity to HBV from vaccination or from previous infection should know their HBsAg status and, if that is positive, should also know their HBeAg status.

--HCWs who are infected with HIV or HBV (and are HBeAg positive) should not perform exposure-prone procedures unless they have sought counsel from an expert review panel and been advised under what circumstances, if any, they may continue to perform these procedures.* Such circumstances would include notifying prospective patients of the HCW's seropositivity before they undergo exposure-prone invasive procedures.

--Mandatory testing of HCWs for HIV antibody, HBsAg, or HBeAg is not recommended. The current assessment of the risk that infected HCWs will transmit HIV or HBV to patients during exposure-prone procedures does not support the diversion of resources that would be required to implement mandatory testing programs. Compliance by HCWs with recommendations can be increased through education, training, and appropriate confidentiality safeguards.

*The review panel should include experts who represent a balanced perspective. Such experts might include all of the following: a) the HCW's personal physician(s), b) an infectious disease specialist with expertise in the epidemiology of HIV and HBV transmission, c) a health professional with expertise in the procedures performed by the HCW, and d) state or local public health official(s). If the HCW's practice is institutionally based, the expert review panel might also include a member of the infection-control committee, preferably a hospital epidemiologist. HCWs who perform exposure-prone procedures outside the hospital/institutional setting should seek advice from appropriate state and local public health officials regarding the review process. Panels must recognize the importance of confidentiality and the privacy rights of infected HCWs. HCWS WHOSE PRACTICES ARE MODIFIED BECAUSE OF HIV OR HBV STATUS

HCWs whose practices are modified because of their HIV or HBV infection status should, whenever possible, be provided opportunities to continue appropriate patient-care activities. Career counseling and job retraining should be encouraged to promote the continued use of the HCW's talents,

knowledge, and skills. HCWs whose practices are modified because of HBV infection should be reevaluated periodically to determine whether their HBeAg status changes due to resolution of infection or as a result of treatment (44). NOTIFICATION OF PATIENTS AND FOLLOW-UP STUDIES

The public health benefit of notification of patients who have had exposure-prone procedures performed by HCWs infected with HIV or positive for HBeAg should be considered on a case-by-case basis, taking into consideration an assessment of specific risks, confidentiality issues, and available resources. Carefully designed and implemented follow-up studies are necessary to determine more precisely the risk of transmission during such procedures. Decisions regarding notification and follow-up studies should be made in consultation with state and local public health officials. ADDITIONAL NEEDS

- Clearer definition of the nature, frequency, and circumstances of blood contact between patients and HCWs during invasive procedures.
- Development and evaluation of new devices, protective barriers, and techniques that may prevent such blood contact without adversely affecting the quality of patient care.
- More information on the potential for HIV and HBV transmission through contaminated instruments.
- Improvements in sterilization and disinfection techniques for certain reusable equipment and devices.
- Identification of factors that may influence the likelihood of HIV or HBV transmission after exposure to HIV- or HBV-infected blood.

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44. Perrillo RP, Schiff ER, Davis GL, et al. A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. N Engl J Med 1990;323:295-301. APPENDIX Definition of Invasive Procedure

An invasive procedure is defined as ``surgical entry into tissues, cavities, or organs or repair of major traumatic injuries" associated with any of the following: ``1) an operating or delivery room, emergency department, or outpatient setting, including both physicians' and dentists' offices; 2) cardiac catheterization and angiographic procedures; 3) a vaginal or cesarean delivery or other invasive obstetric procedure during which bleeding may occur; or 4) the manipulation, cutting, or removal of any oral or perioral tissues, including tooth structure, during which bleeding occurs or the potential for bleeding exists." Reprinted from: Centers for Disease Control. Recommendation for prevention of HIV transmission in health-care settings. MMWR 1987;36 (suppl. no. 2S):6S-7S.

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Recommendations of the U.S. Public Health Service Task Force on the Use of Zidovudine to Reduce Perinatal Transmission of Human Immunodeficiency Virus

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Contents

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Executive Committee and U.S. Public Health Service Task Force

On June 6, 1994, the U.S. Public Health Service convened a workshop in Bethesda, Maryland, to develop recommendations for the use of zidovudine to reduce the risk for perinatal transmission of human immunodeficiency virus (HIV). The recent results of AIDS Clinical Trials Group Protocol 076, a controlled clinical trial sponsored by the National Institutes of Health in collaboration with the National Institute of Health and Medical Research and the National Agency of Research on AIDS in France, indicate that zidovudine administered to a selected group of HIV-infected women and their infants can reduce the risk for perinatal transmission of HIV by approximately two-thirds. The implications of these results for use of zidovudine in HIV-infected pregnant women and neonates were discussed at the workshop. The following persons participated in the workshop and either served as the Executive Committee writing group that developed the recommendations or were members of the U.S. Public Health Service Task Force on the Use of Zidovudine to Reduce Perinatal HIV Transmission.

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Recommendations of the U.S. Public Health Service Task Force on the Use of Zidovudine to Reduce Perinatal Transmission of Human Immunodeficiency Virus

Summary

*These recommendations update the interim guidelines (*1*) developed by the U.S. Public Health Service for the use of zidovudine (ZDV) to reduce the risk for perinatal transmission of human immunodeficiency virus (HIV) infection. The recently reported results of AIDS Clinical Trials Group Protocol 076 demonstrated that ZDV administered to a selected group of HIV-infected pregnant women and their infants can reduce the risk for perinatal HIV transmission by approximately two-thirds. The regimen used in this trial included antenatal oral administration of ZDV beginning at 14–34 weeks of gestation and continuing throughout pregnancy, followed by intrapartum intravenous ZDV and postnatal oral administration of ZDV to the infant for 6 weeks after delivery.*

This document summarizes the results of the trial, discusses limitations in the interpretation of the results, reviews the potential long-term adverse effects of this ZDV regimen for infants and women, and provides recommendations for the use of ZDV to reduce perinatal transmission and for medical monitoring of pregnant women and infants receiving this therapy. Because the clinical status of many HIV-infected women may differ from that of the women in this trial, the recommendations should be tailored to each woman's clinical situation. The potential benefits, unknown long-term effects, and gaps in knowledge about her specific clinical situation must be discussed with the woman. This information is intended to provide a basis for discussion between the woman and her health-care provider so that the woman can weigh the risks and benefits of such therapy and make informed decisions about her treatment.

INTRODUCTION

Worldwide, perinatal (i.e., mother-to-infant) transmission accounts for most human immunodeficiency virus (HIV) infections among children. In the United States, approximately 7,000 infants, 1,000–2,000 of whom are HIV infected, are born to HIV-infected women each year (*2*). In the United States, HIV is currently the seventh leading cause of death in children 1–4 years of age (*3*) and the fourth among women 25–44 years of age (*4*).

The ideal approach to reducing perinatal transmission is to prevent HIV infection among women. However, despite ongoing efforts to provide education about HIV prevention, the incidence of infections among women of reproductive age in the United States is increasing in some areas (*2*). In the United States, where safe alternatives to breast milk are available, HIV-infected women are advised to refrain from breastfeeding to avoid postnatal transmission of HIV to their infants (*5*). However, refraining

from breastfeeding will not prevent transmission occurring in utero or intrapartum, and strategies to reduce transmission during these periods are being evaluated.

The recently reported interim results of the Acquired Immunodeficiency Syndrome (AIDS) Clinical Trials Group (ACTG) Protocol 076, a clinical trial sponsored by the National Institutes of Health in collaboration with the National Institute of Health and Medical Research and the National Agency of Research on AIDS in France, indicate that zidovudine (ZDV) administered to a selected group of HIV-infected pregnant women and their infants can reduce the risk for perinatal HIV transmission by approximately two-thirds (*1,6*). This use of ZDV has the potential to substantially reduce the rate of perinatal transmission, which would reduce overall child mortality. However, the results of this study are directly applicable only to HIV-infected women with characteristics similar to those of the women who entered the study, and the long-term risks of ZDV used in this manner are not known.

On June 6–7, 1994, the U.S. Public Health Service convened a workshop, "Use of ZDV to Prevent Perinatal HIV Transmission (ACTG Protocol 076): Workshop on Implications for Treatment, Counseling, and HIV Testing." The medical, scientific, public health, and legal communities and interested professional, community, and advocacy organizations were represented. The workshop addressed two issues related to the results of ACTG Protocol 076: a) treatment recommendations for the use of ZDV to reduce perinatal transmission of HIV and b) the implications of the trial results for HIV counseling and testing.

This report summarizes the conclusions of the workshop with regard to the use of ZDV to reduce perinatal transmission, provides recommendations for treatment options for HIV-infected pregnant women and their newborns and medical monitoring for pregnant women and neonates receiving ZDV, and discusses issues related to long-term follow-up of women and their children who have received ZDV.

BACKGROUND

Summary of Results of ACTG Protocol 076

On February 21, 1994, the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Child Health and Human Development announced the interim results of a randomized, multicenter, double-blind, placebo-controlled clinical trial, ACTG Protocol 076. Eligible participants were HIV-infected pregnant women at 14–34 weeks of gestation who had received no antiretroviral therapy during their current pregnancy, had no clinical indications for antepartum antiretroviral therapy, and had CD4+ T-lymphocyte counts $\geq$200/μL at the time of entry into the study (Box 1). The study began in April 1991; as of December 20, 1993, the time of the interim analysis, 477 women had been enrolled and 421 infants born. The racial/ethnic distribution of the HIV-infected women enrolled in the trial was similar to that of the total population of HIV-infected women in the United States.

Enrolled women were assigned randomly to receive a regimen of either ZDV or placebo. The ZDV regimen included oral ZDV initiated at 14–34 weeks of gestation and continued throughout the pregnancy, followed by intravenous ZDV during labor and oral administration of ZDV to the infant for 6 weeks after delivery (Box 2). The placebo regimen was administered identically. Blood specimens were obtained for HIV culture

BOX 1. Eligibility criteria for HIV-infected pregnant women participating in AIDS Clinical Trials Group Protocol 076

- Pregnancy at 14–34 weeks of gestation.
- No antiretroviral therapy during the current pregnancy.
- No clinical indications for antenatal antiretroviral therapy.
- CD4+ T-lymphocyte count ≥200 cells/μL at the time of entry into the study.

BOX 2. Zidovudine regimen from AIDS Clinical Trials Group Protocol 076

- Oral administration of 100 mg of zidovudine (ZDV) five times daily, initiated at 14–34 weeks of gestation and continued throughout the pregnancy.
- During labor, intravenous administration of ZDV in a 1-hour loading dose of 2 mg per kg of body weight, followed by a continuous infusion of 1 mg per kg of body weight per hour until delivery.
- Oral administration of ZDV to the newborn (ZDV syrup at 2 mg per kg of body weight per dose every 6 hours) for the first 6 weeks of life, beginning 8–12 hours after birth.

from all infants at birth and at 12, 24, and 78 weeks of age. A positive viral culture was considered indicative of HIV infection. Sera from the infants at 15 and 18 months of age also were tested for HIV antibody.

The Kaplan-Meier method (*7*) was used to estimate the rate of perinatal transmission at 18 months of age among the 364 children whose HIV infection status was known on the basis of culture and who therefore were included in the interim analysis. The estimated transmission rate was 25.5% among the 184 children in the placebo group (95% confidence interval [CI]=18.4%–32.5%), compared with 8.3% among the 180 children in the ZDV group (95% CI=3.9%–12.8%). The difference in the estimated transmission rate between the two groups was statistically significant (p=0.00006). ZDV treatment did not appear to delay the diagnosis of HIV infection.

Observed toxicity specifically attributable to ZDV was minimal among the women in this study. Adverse effects such as anemia, neutropenia, thrombocytopenia, and liver chemistry abnormalities were reported as frequently among women receiving placebo as among women receiving ZDV. Six women—three in each treatment group—discontinued therapy because of toxicity attributed to the study drug. The women were evaluated at 6 weeks and 6 months postpartum. A statistically significant increase in CD4+ T-lymphocyte count from baseline to 6 weeks postpartum was observed for women in both ZDV and placebo treatment groups; this increase was greater among women in the ZDV group. At 6 months postpartum, the CD4+ T-lymphocyte counts for both groups had decreased to similar levels. CD4+ T-lymphocyte counts decreased to <200/μL in only four women, including one receiving ZDV and three receiving placebo. No women died during the study.

Serial sonographic evaluations for fetal growth and amniotic fluid volume as conducted in the study (at entry and every 4 weeks from 28 weeks of gestation until delivery) demonstrated no differences between pregnancies in women who had received placebo or ZDV. Birth parameters (gestational age; birth weight, length, and head circumference; and Apgar scores) were similar among infants born to women in either group. The median birth weight was 3,160 g (range: 1,040–5,267 g), and the median gestational age at birth was 39 weeks (range: 27–43 weeks). No statistically significant difference was observed between the ZDV and placebo groups in the number of infants with birth weight <2,500 g, who were small or large for gestational age, or who were born prematurely. The occurrence of major or minor congenital abnormalities was approximately equal between the two groups, and no pattern in the type of abnormalities was observed.

The infants in the study tolerated the ZDV therapy well. The only adverse effect observed more frequently among infants in the ZDV treatment group was mild, transient anemia. Hemoglobin values for infants in the group receiving ZDV were lower than for the group receiving placebo, with a maximum mean difference of 1 gm/dL occurring at 3 weeks of age. The lowest mean hemoglobin value in infants receiving ZDV occurred at 6 weeks of age and resolved without therapy for anemia after the infants had completed the ZDV treatment. The hemoglobin values of infants receiving ZDV were similar to those of placebo recipients by 12 weeks of age. The incidence of neutropenia and serum chemistry abnormalities was similar between ZDV and placebo groups of infants, and no difference in the pattern of chemistry abnormalities was observed.

Based on these interim findings, NIAID accepted the recommendation of its independent data and safety monitoring board to terminate enrollment into the trial and to offer ZDV to women in the placebo group who had not yet delivered and to their infants up to 6 weeks of age.* Follow-up of patients enrolled in the study is ongoing.

Limitations in Interpretation and Extrapolation of ACTG Protocol 076 Results

This clinical trial demonstrated that the ACTG Protocol 076 ZDV regimen can substantially reduce perinatal HIV transmission. However, several important limitations should be noted. First, perinatal HIV transmission was still observed despite drug therapy. Second, the efficacy of this therapy is unknown for HIV-infected pregnant women who have advanced disease, who have received prior antiretroviral therapy, or who have ZDV-resistant virus strains. Third, although the ZDV regimen used in this trial was not associated with serious short-term adverse effects, such effects may be observed when this use of ZDV becomes more widespread. Fourth, the long-term risks for the child associated with exposure to ZDV in utero and early infancy have not been determined. Fifth, it is not known if use of ZDV during pregnancy will affect the drug's efficacy for the woman when it becomes clinically indicated for her own health.

Further complicating the incorporation of this ZDV regimen into clinical practice is the fact that some HIV-infected women seek medical care late in pregnancy or when

*A summary of the study's findings is available from the AIDS Clinical Trials Information Service at 1(800)TRIALS-A (1[800]874-2572).

they are already in labor, when the full ZDV regimen used in ACTG Protocol 076 cannot be administered. Moreover, many pregnant women are not aware that they are HIV infected, are not tested before or during pregnancy, and remain undiagnosed. As a result, they do not receive information about therapy that could reduce the risk for HIV transmission to their infants.

Potential Long-Term Adverse Effects of ZDV Administered During Pregnancy

The long-term effects of ZDV treatment during pregnancy solely to reduce perinatal transmission or of fetal and neonatal exposure to ZDV are not known. ZDV is a nucleoside analog that inhibits HIV replication by interfering with HIV RNA-dependent DNA polymerase. ZDV triphosphate also can inhibit human cellular DNA polymerases, but only at concentrations much higher than those required to inhibit HIV polymerase. However, gamma DNA polymerase, which is required for mitochondrial replication, may be inhibited by ZDV at concentrations nearer to those that can be achieved in vivo.

Concerns related to the potential long-term toxicity of nucleoside analogs include potential mutagenic and carcinogenic effects, possible effects on tissues with high mitochondrial content (such as hepatic and cardiac tissue), possible teratogenicity, and possible effects on the reproductive system.

ZDV has been shown to be a mutagen in vitro, and, in a mammalian in vitro cell transformation assay, ZDV was positive at concentrations of ≥0.5 μg/mL (*8*). Noninvasive squamous epithelial vaginal tumors were produced after 19–21 months of continuous dosing in 12% of mice administered a dosage equivalent to three times the estimated human exposure at the recommended therapeutic dosage. Similar findings were observed in 3% of rats that received 24 times the recommended therapeutic dosage. Carcinogenicity studies in rodents, however, may not be predictive of human experience.

In humans, an increased incidence of non-Hodgkin's lymphoma has been reported in HIV-infected men receiving ZDV, but this increase probably reflects longer survival despite severe immunodeficiency rather than a direct effect of ZDV (*9*). The potential for carcinogenesis should be further assessed through continued follow-up of children who were exposed to ZDV in utero.

Myopathy and cardiomyopathy have been associated with ZDV therapy. In an individual patient, the effects secondary to ZDV are often difficult to distinguish from those of HIV infection. A prospective study of HIV-infected children demonstrated no effect of ZDV therapy on cardiac function (*10*).

Reproductivity/fertility studies in animals have demonstrated no adverse effects of ZDV on either the fertility of male or female rats or the reproductive capacity of their offspring (*11*). ZDV administered to mice early in gestation was associated with an embryotoxic effect and fetal resorptions; however, ZDV administered at or beyond midgestation had no detectable effect on the fetus (*12,13*).

ZDV is assigned pregnancy category C status by the Food and Drug Administration (FDA).* Most studies of ZDV administered to pregnant animals have not demonstrated teratogenicity. In one study, pregnant rats were administered toxic doses of ZDV during organogenesis (i.e., equivalent to approximately 50 times the recommended daily clinical dose, based on relative body surface areas); developmental malformations and skeletal abnormalities were observed in 12% of fetuses (*14*).

In humans, observational studies involving small numbers of subjects have demonstrated no apparent association of fetal malformations with antenatal ZDV use (*15–19*). In ACTG Protocol 076, the incidence of congenital malformations was similar for ZDV and placebo recipients. However, because ZDV was not administered until after 14 weeks of gestation in this study, the potential teratogenicity of ZDV administered during the first trimester cannot be assessed. Similarly, in a recent report from the Antiretroviral Pregnancy Registry maintained by the Wellcome Foundation and Hoffman LaRoche in conjunction with CDC, no increase in the risk of congenital abnormalities above that expected for all pregnancies was observed among infants born to 121 prospectively registered HIV-infected women who received ZDV during pregnancy, nor was there any unusual pattern of birth defects (*20*).

Use of ZDV during pregnancy could be associated with the development of ZDV-resistant virus, which may lessen the drug's therapeutic benefit for the woman when it is needed for her own health. However, patients with early-stage HIV disease rarely develop ZDV-resistant strains before they have received 18–24 months of continuous therapy (*21*). After discontinuation of ZDV therapy, an increase in ZDV-susceptible isolates has been observed in some patients who had ZDV-resistant isolates while they were receiving ZDV, although resistance to ZDV has been reported to persist for more than a year after therapy was discontinued (*22,23*). Because the development of ZDV-resistant viral strains secondary to transient ZDV use during pregnancy is a theoretical concern, considerations for the woman's future health care should include the availability of alternative drugs for treatment of HIV infection.

GENERAL PRINCIPLES REGARDING TREATMENT RECOMMENDATIONS

The following treatment recommendations have been formulated to provide a basis for discussion between the woman and her health-care provider about the use of ZDV to reduce perinatal transmission. HIV-infected women should be informed of the substantial benefit and short-term safety of ZDV administered during pregnancy and the neonatal period observed in ACTG Protocol 076. However, they also must be

*FDA pregnancy categories are: A, in which adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk during later trimesters); B, in which animal reproduction studies fail to demonstrate a risk to the fetus and adequate and well-controlled studies of pregnant women have not been conducted; C, in which safety in human pregnancies has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus; D, in which there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks; and X, in which studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

informed that the long-term risks of ZDV therapy to themselves and their children are unknown. A woman's decision to use ZDV to reduce the risk for HIV transmission to her infant should be based on a balance of the benefits and potential risks of the regimen to herself and to her child.

Discussion of treatment options should be noncoercive, and the final decision to accept or reject ZDV treatment recommended for herself and her child is the right and responsibility of the woman. A decision not to accept treatment should not result in punitive action or denial of care, nor should ZDV be denied to a woman who decides to receive the regimen.

Various circumstances that commonly occur in clinical practice are described and the factors influencing treatment considerations are highlighted in the following discussion (Box 3). All potential clinical situations cannot be enumerated, and, in many cases, definitive evidence upon which to base a recommendation is not currently available. Therefore, each pregnant woman and her health-care provider must consider the potential benefits, unknown long-term effects, and gaps in knowledge relating to her clinical situation. Furthermore, health-caregivers and institutions should provide culturally, linguistically, and educationally appropriate information and counseling to the HIV-infected woman so that she can make informed decisions.

CLINICAL SITUATIONS AND RECOMMENDATIONS FOR USE OF ZDV TO REDUCE PERINATAL TRANSMISSION

Clinical Situation Meeting the Entry Criteria for ACTG Protocol 076

I. Pregnant HIV-infected women with CD4+ T-lymphocyte counts ≥200/μL who are at 14–34 weeks of gestation and who have no clinical indications for ZDV and no history of extensive (>6 months) prior antiretroviral therapy.

Discussion:

The results of ACTG Protocol 076 are directly applicable only to women who meet the entry criteria for the study (Table 1). The data from that study indicate that the complete ACTG Protocol 076 ZDV regimen will likely reduce the risk for perinatal transmission by about two-thirds.

Because this study was randomized and placebo controlled, entry was restricted to women who had no clinical indications for ZDV use for their own health and who had CD4+ T-lymphocyte counts ≥200/μL. Prior ZDV use during the current pregnancy resulted in exclusion from the study. Few women (4%) had received ZDV before the current pregnancy, and most of that therapy was of limited duration.

Women were not enrolled either before the 14th week or after the 34th week of gestation. The rationale for exclusion before 14 weeks of gestation was to preclude ZDV exposure during fetal organogenesis. The 34-week limit allowed most women to receive several weeks of ZDV before delivery to allow time for a decrease in maternal viral load (a presumed important determinant of transmission risk).

Although ZDV was successful in reducing perinatal transmission, the study regimen did not completely prevent it. The possible reasons for transmission to

these infected infants are being evaluated but have not yet been identified. Several case reports also have described perinatal transmission despite the initiation of ZDV therapy during pregnancy (*24–27*).

Although long-term toxicity to infants is unknown, this risk must be weighed against the decreased risk for transmission of an infection associated with substantial risk of death. Currently, there is no way to predict if an individual pregnancy will be associated with HIV transmission; therefore, each fetus must be considered to have an estimated 25% risk of a life-threatening infection. Because ZDV therapy reduced the rate of transmission by two-thirds (from 25.5% to 8.3%), any long-term toxicity related to ZDV would have to be severe (e.g., malignancy or profound developmental delay) and relatively common among ZDV-exposed infants to outweigh the substantial benefit.

Recommendation:

The health-care provider should recommend the full ACTG Protocol 076 regimen to all HIV-infected pregnant women in this category. This recommendation should be presented to the pregnant woman in the context of a risk-benefit discussion: a reduced risk of transmission can be expected, but the long-term adverse consequences of the regimen are not known. The decision about this regimen should be made by the woman after discussion with her health-care provider.

Clinical Situations Not Meeting the Study Entry Criteria

Information about the benefit and short-term risks of ZDV therapy is applicable from this trial only for women who meet the entry criteria of the study. Recommendations about use of the ZDV regimen for women whose clinical conditions differ from the ACTG Protocol 076 eligibility criteria were derived from consensus interpretation of available scientific data.

II. Pregnant HIV-infected women who are at >34 weeks of gestation, who have no history of extensive (>6 months) prior antiretroviral therapy, and who do not require ZDV for their own health.

Discussion:

This patient population has clinical characteristics similar to those of women enrolled in ACTG Protocol 076; the major difference is gestational age at which ZDV therapy would begin. Therefore, the ZDV regimen for these women would differ from the ACTG Protocol 076 regimen only in duration of antenatal therapy. As much as 50%–70% of perinatal transmission may occur close to or during delivery (28). Therefore, the ACTG Protocol 076 ZDV regimen may have some benefit when initiated at >34 weeks of gestation, although the intervention is likely to decrease in effectiveness as the duration of antenatal ZDV administration is reduced. A study evaluating the effect of ZDV on quantitative p24 antigen levels indicates that maximal effect is observed after 8–16 weeks of therapy (*29*). A shorter duration of ZDV therapy may thus be associated with an effect on maternal viral load that is less than can be anticipated when ZDV is initiated before 34 weeks of gestation. Both potential risks and benefits for the woman and her infant may decrease the closer to delivery that the ZDV regimen is initiated.

Further clinical trials should be designed to assess the efficacy of interventions that are initiated late in the third trimester for preventing perinatal transmission.

Recommendation:

The health-care provider should recommend the full ACTG Protocol 076 regimen in the context of a risk-benefit discussion with the pregnant woman. The woman should be informed that ZDV therapy may be less effective than that observed in ACTG Protocol 076, because the regimen is being initiated late in the third trimester.

III. Pregnant HIV-infected women with CD4+ T-lymphocyte counts <200/μL who are at 14–34 weeks of gestation, who have no other clinical indications for ZDV, and who have no history of extensive (>6 months) prior antiretroviral therapy.

Discussion:

Women in this group meet the current standard of care for ZDV treatment of HIV infection for their own benefit (*30,31*); therefore, administration of ZDV during pregnancy for these women provides direct benefit to them as well as potential benefit to their infants. The risk for HIV transmission to the infants of HIV-infected pregnant women with low CD4+ T-lymphocytes or percent of total lymphocytes ranges from 22% to 60% (*32–38*).Viral load has been shown to increase as CD4+ T-lymphocyte count decreases (*39*); thus, baseline viral loads can be expected to be high among the women in this group.

Although viral replication and resultant capacity for mutations in this group are high, preexisting ZDV-resistant viral strains are unlikely to be present because these women have had little or no exposure to ZDV. Therefore, ZDV therapy can be expected to result in an acute reduction in maternal viral load analogous to that observed in women who have CD4+ T-lymphocyte counts ≥200/μL. Additionally, the mother's CD4+ T-lymphocyte count would not be expected to affect ZDV levels or toxicity in the infant after administration of ZDV during labor and the first 6 weeks of life. Hence, maternal CD4+ T-lymphocyte count should not affect the potential utility of neonatal levels of systemic ZDV for reducing intrapartum transmission.

Although this population of pregnant women was not studied in ACTG Protocol 076, addition of the intrapartum and neonatal components of the ACTG Protocol 076 ZDV regimen to antenatal maternal therapy may reduce the risk for HIV transmission. However, the magnitude of the effect of ZDV on reducing the transmission rate in this group may not be the same as that demonstrated in ACTG Protocol 076 for women with CD4+ T-lymphocyte counts ≥200. Further clinical trials should assess the utility of interventions in this group of women. Because ZDV therapy is clinically indicated for these women for their own health, the additional risk of the remainder of the ACTG Protocol 076 regimen is the discomfort to the woman of another intravenous infusion during labor and the possible effects of the additional 6 weeks of ZDV exposure for the infant.

Recommendation:

The health-care provider should recommend initiation of antenatal ZDV therapy to the woman for her own health benefit (*31*). The intrapartum and neonatal

components of the ACTG Protocol 076 regimen should be recommended until further information becomes available. This recommendation should be presented in the context of a risk-benefit discussion with the pregnant woman.

IV. Pregnant HIV-infected women who have a history of extensive (>6 months) ZDV therapy and/or other antiretroviral therapy before pregnancy.

Discussion:

Women who have received extensive prior ZDV therapy may be infected with viral strains with reduced susceptibility to ZDV. These resistant strains of HIV can be transmitted from mother to fetus; however, the frequency with which such transmission occurs is unknown.

Resistant virus appears to emerge more quickly if therapy is initiated at later stages of HIV disease (*21*). The appearance of mutations associated with ZDV resistance follows a temporal pattern, and the level of in vitro resistance is proportional to the number of mutations in the reverse transcriptase-coding region of HIV (*40*). Phenotypically and genotypically diverse HIV populations can coexist in patients who are receiving ZDV therapy.

In one study, ZDV-resistant strains appeared earlier during ZDV therapy in patients with advanced HIV disease than in patients whose ZDV therapy was initiated at an early stage of the disease. After 12 months of ZDV therapy, viral isolates from 89% of patients with late-stage disease and 31% of those with early-stage disease were resistant (*21*). However, isolates from only 33% of late-stage patients demonstrate high-level resistance (defined as a 100-fold decrease in susceptibility [*41*]). Resistant virus also was more likely to be isolated from patients who had low CD4+ T-lymphocyte counts when therapy was initiated: 1-year estimated rates of resistance in patients with baseline CD4+ T-lymphocyte counts of >400, 100–400, and <100 cells/μL were 27%, 41%, and 89%, respectively. In patients with advanced disease, high-level resistance develops after 6–18 months of therapy. However, in patients with early-stage disease, high-level resistance appears to be delayed until after 24 months of therapy (*22*). Therefore, ZDV-resistant strains are likely to be more common in women with advanced disease who have received prolonged therapy.

ZDV-resistant viral strains also may be more common in persons receiving alternative antiretroviral agents because their disease progressed while they were receiving ZDV therapy. There is controversy regarding the association of clinical disease progression during ZDV therapy with the development of ZDV resistance and regarding whether resistance persists when therapy is changed to an alternative antiretroviral agent (*41*). Some studies involving small numbers of children have indicated that in vitro susceptibility to ZDV is correlated with clinical outcome, suggesting that ZDV-resistant isolates are associated with diminished efficacy of ZDV and more rapid clinical progression (*42,43*). However, at least one study indicated that disease progression may be associated more closely with the development of syncytia-inducing viral phenotype than with resistance to ZDV (*44*). Change to alternative antiretroviral therapy has been associated with reversal of ZDV resistance in some studies, but resistance has been reported to persist for considerable periods of time after discontinuation of ZDV (*23,45*). The prevalence of ZDV-resistant viral strains in women

who are receiving alternative antiretroviral agents because of disease progression has not been defined.

The capability of ZDV to reduce HIV transmission may be decreased for mothers in whom ZDV-resistant strains predominate, particularly if the strains have high-level resistance; however, this assumption is not yet supported by data. Further clinical trials to evaluate alternative approaches for such women are needed.

Recommendation:

Because data are insufficient to extrapolate the potential efficacy of the ACTG Protocol 076 regimen for this population of women, the health-care provider should consider recommending the ACTG Protocol 076 regimen on a case-by-case basis after a discussion of the risks and benefits with the pregnant woman. Issues to be discussed include her clinical and immunologic stability on ZDV therapy, the likelihood that she is infected with a ZDV-resistant HIV strain, and, if relevant, the reasons for her current use of an alternative antiretroviral agent (e.g., lack of response to or intolerance of ZDV therapy). Consultation with experts in HIV infection may be warranted. The health-care provider should make the ACTG Protocol 076 regimen available to the woman, although its effectiveness may vary depending on her clinical status.

V. Pregnant HIV-infected women who have not received antepartum antiretroviral therapy and who are in labor.

Discussion:

Data from studies in humans are insufficient to evaluate the potential effectiveness of ZDV in this situation. Because the mother's exposure to ZDV would be brief, such therapy can be expected to have no effect on the level of maternal virus in blood or genital secretions. However, because of the intravenous loading dose and continuous infusion of ZDV during labor, the infant will be born with circulating levels of ZDV similar to those of infants whose mothers have received antenatal as well as intrapartum ZDV. ZDV may have some utility for this group of patients—regardless of whether the pregnancy is at term or preterm—because the presence of systemic levels of ZDV in the infant before or shortly after HIV exposure through contact with the mother's blood and genital secretions during delivery may help prevent intrapartum transmission.

The intravenous route was chosen for drug dosing during labor in ACTG Protocol 076 because continuous intravenous infusion of drug after an initial loading dose results in predictable levels of ZDV in the mother. Under optimal circumstances, these maternal levels provide a substantial fetal blood level during birth, when the infant is presumed to be exposed extensively to HIV through contact with the mother's blood and genital secretions. Because gastric emptying is delayed during labor, the absorption of orally administered drugs is unpredictable (*46*). Therefore, oral administration of ZDV during labor might produce widely variable systemic levels in the mother and infant. Oral ZDV administered intrapartum cannot be assumed to be equivalent to the intravenous intrapartum ZDV component used in ACTG Protocol 076. Further studies are needed to characterize the pharmacokinetics of oral ZDV during labor.

Intrapartum ZDV cannot prevent the substantial number of infections that occur before labor (*26*). Therefore, ZDV administered only during labor and to the newborn may not be effective.

Because the mother would receive ZDV only during labor, her risk for developing resistant virus or ZDV toxicity would be minimal. The primary risk is that associated with an intravenous catheter. The risk to the infant would be limited to the potential toxicity associated with transfer of drug from the maternal intrapartum infusion and with 6 weeks of oral ZDV therapy, without in utero exposure to the drug. The effect of neonatal ZDV treatment in ameliorating disease progression in infected infants is unknown. Clinical trials should be designed to address the efficacy of antiretroviral therapy in this situation.

Recommendation:

For women with HIV infection who are in labor and who have not received the antepartum component of the ACTG Protocol 076 regimen (either because of lack of prenatal care or because they did not wish to receive antepartum therapy), the health-care provider should discuss the benefits and potential risks of the intrapartum and neonatal components of the ACTG Protocol 076 regimen and offer ZDV therapy when the clinical situation permits.

VI. Infants who are born to HIV-infected women who have received no intrapartum ZDV therapy.

Discussion:

Infants whose mothers have not received ZDV during late pregnancy and/or labor will not have circulating ZDV levels during birth, a period of presumed viral exposure. Data are insufficient to allow assessment of the potential efficacy of postexposure prophylaxis with ZDV in this situation. Studies of postexposure prophylaxis of retroviral infection with ZDV in animal models have yielded inconclusive results. Additionally, studies involving animal models should be interpreted with caution: many of these studies have involved nonhuman retroviruses that may have different pathogenic mechanisms from those of HIV, used methods of viral inoculation that are not relevant to perinatal transmission (e.g., intrathymic injection), and/or used a massive inoculum of virus (*47*).

The limited data from animal studies indicate that if ZDV is to have any effect as postexposure prophylaxis, prompt administration (within hours) is important, and that even with early initiation of ZDV, such prophylaxis may not be protective. In a SCID-hu mouse model of HIV infection (an immune-deficient model reconstituted with human cells), a time-dependent suppression of HIV replication was observed with ZDV prophylaxis (*48*). When ZDV was administered within 2 hours of viral inoculation, viral replication was not detectable at 2 weeks after inoculation in all treated animals; when ZDV was administered 2–36 hours after inoculation, rates of viral detection at 2 weeks increased in proportion to increasing time since ZDV was administered; and when ZDV was administered 48 hours after inoculation, virus was detectable in all animals (*48*). Therefore, whether the effect of ZDV therapy is prevention or suppression of infection cannot be established. In several animal model systems, ZDV administration was observed only to suppress or ameliorate retroviral infection (*49–51*).

At least 13 reports have described the failure of prophylactic ZDV to prevent HIV infection in humans following exposure to HIV-infected blood, even though the drug was administered promptly after exposure (*52*). Although these anecdotal reports do not establish that ZDV therapy is ineffective as postexposure prophylaxis, its efficacy can be expected to be lower in this situation than with the full regimen. Further studies are needed to evaluate whether a therapy administered only during the neonatal period can effectively prevent perinatal transmission.

Recommendation:

If the clinical situation permits and if ZDV therapy can be initiated within 24 hours of birth, the health-care provider should offer the ACTG Protocol 076 postpartum component of 6 weeks of neonatal ZDV therapy for the infant in the context of a risk-benefit discussion with the mother. Data from animal prophylaxis studies indicate that, if ZDV is administered, therapy should be initiated as soon as possible (within hours) after delivery. If therapy cannot begin until the infant is >24 hours of age and the mother did not receive therapy during labor, no data support offering therapy to the infant.

RECOMMENDATIONS FOR MONITORING THE ZDV REGIMEN FOR MOTHERS AND INFANTS

Women and their children should receive care together in a family-centered setting. Care should be coordinated between gynecologic, pediatric, internal medicine, infectious disease, and other health-care specialists to ensure that both mother and child receive appropriate medical follow-up. A comprehensive program of support services is necessary to ensure that both mother and child continue to receive health care.

Maternal Monitoring

HIV-infected pregnant women should be monitored in accordance with previously published guidelines (*31,53*). Monitoring during pregnancy should include monthly assessment for ZDV-associated hematologic and liver chemistry abnormalities. Indications of toxicity that might require interrupting or stopping the dose of ZDV include a) hemoglobin <8 gm/dL, b) absolute neutrophil count <750 cells/μL, or c) AST (SGOT) or ALT (SGPT) greater than five times the upper limit of normal.

CD4+ T-lymphocyte counts should be monitored to determine if prophylaxis for opportunistic infections, such as *Pneumocystis carinii* pneumonia (PCP), should be initiated. Pregnant HIV-infected women with CD4+ T-lymphocyte counts <200 cells/μL should receive appropriate PCP prophylaxis. If the CD4+ T-lymphocyte count is <600 cells/μL, the evaluation should be repeated each trimester. CD4+ T-lymphocyte counts should be measured at 6 weeks and 6 months postpartum to evaluate if antiretroviral therapy is indicated.

Fetal Monitoring

Antepartum testing, including sonographic and nonstress testing and intrapartum fetal monitoring, should be performed only as clinically indicated, not specifically because the patient is being treated with ZDV during pregnancy.

Infant Monitoring

A complete blood count and differential should be performed at birth as a baseline evaluation. Repeat measurements of hemoglobin are recommended at 6 and 12 weeks of age. ZDV should be administered with caution to infants born with severe anemia (hemoglobin <8 gm/dL), and treatment of the anemia and intensive monitoring are warranted if the drug is administered.

Previously published guidelines contain recommendations for diagnosing HIV infection in infants and for initiating PCP prophylaxis and antiretroviral therapy for those who are infected (*53–55*). The potential efficacy of ZDV therapy for HIV-infected children who require antiretroviral therapy and who received ZDV in utero and during early infancy has not been determined. A specialist in pediatric HIV infection may be consulted if therapy is necessary for infected children whose mothers received ZDV during pregnancy. Further research is needed to describe the response to therapy and progression of disease in such infants.

POTENTIAL LONG-TERM EFFECTS OF ZDV THERAPY FOR MOTHERS AND INFANTS AND RECOMMENDATIONS FOR FOLLOW-UP

Discussion

Observational data about the pregnancy outcomes of women who receive ZDV during pregnancy are being collected through the Antiretroviral Pregnancy Registry. The purpose of the registry is to provide surveillance for possible teratogenicity among infants born to women who received ZDV during pregnancy. Health-care providers can register such patients by calling the registry at (800) 722-9292, extension 8465, in the United States or (919) 315-8465 outside the United States. Written reports are available from Antiretroviral Pregnancy Registry, P.O. Box 12700, Research Triangle Park, NC 27709.

Concerns about the potential long-term adverse effects among women include development of ZDV-resistant virus when ZDV therapy is used intermittently to reduce perinatal transmission, particularly during more than one pregnancy, and the potential effect such resistance could have on disease progression for the woman. Although results of studies have demonstrated an association between emergence of ZDV resistance and total duration of ZDV exposure, none of the study designs has specifically addressed the effect of intermittent therapy on development of resistance.

Continued follow-up of the women who participated in ACTG Protocol 076 and of their infants is planned. A protocol to provide prospective evaluation of the health of the women enrolled in ACTG Protocol 076 is being designed by the Women's Health Committee of the ACTG. This protocol will evaluate virologic, immunologic, and clinical parameters among participating women.

Data are insufficient to address any effect that exposure to ZDV in utero might have on risk for neoplasia or organ system toxicities. ACTG Protocol 219 is an ongoing study designed to provide prospective evaluation for children who have been exposed through ACTG protocols to antiretroviral agents in utero or to HIV vaccines until they are 21 years of age. This protocol will provide intensive evaluation of multiple organ

system functions, neuropsychologic testing, and quality of life. Information about the potential long-term effects of the complete or partial ACTG Protocol 076 ZDV regimen on women and children receiving the regimen outside a clinical trial protocol also may be provided from evaluation of federally funded and other prospective studies of HIV-infected women and their infants.

Recommendation:

Additional efforts are required to characterize the long-term effects of the ACTG Protocol 076 ZDV regimen on women and children. The specific issues of viral resistance and disease progression should be addressed among women who receive ZDV during pregnancy solely to reduce perinatal HIV transmission. Monitoring for these HIV-infected women should include Pap smears and gynecologic examinations as recommended in previously published guidelines (*56*), as well as an assessment of the patient's future needs for family planning consultation and services.

Long-term follow-up of both uninfected and infected infants born to mothers receiving ZDV during pregnancy is important. Assessment of organ system toxicities, neurodevelopment, pubertal development, reproductive capacity, and development of neoplasms should be emphasized. Special studies will need to be developed to address these specific concerns, and innovative methods and support systems should be designed to assist in follow-up of these women and their children.

CONCLUSION

The decision by an HIV-infected pregnant woman to use ZDV to reduce the risk for perinatal transmission requires a complex balance of individual benefits and risks that is best accomplished through discussions with her health-care provider. Such discussions should be noncoercive, linguistically and culturally appropriate, and tailored to the patient's educational level.

The recommendations in this report have been developed for use in the United States. Although perinatal transmission of HIV infection is an international problem, alternative strategies may be appropriate in other countries (*57*). The policy and practice in other countries may differ from these recommendations and depend on local considerations, such as availability of ZDV, access to facilities for intravenous infusion during labor, and alternative interventions that may be under evaluation.

These recommendations have been developed in response to the urgent need to provide guidance to women and health-care providers in the United States about the use of ZDV to reduce the risk for perinatal HIV transmission and about the possible adverse outcomes of such ZDV treatment. They have been formulated on the basis of the available data from ACTG Protocol 076 and current information regarding factors associated with transmission. The information on which these recommendations are based is incomplete, and additional information is needed to optimize use of ZDV for this purpose.

The decision to use the ACTG Protocol 076 regimen for preventing perinatal transmission of HIV requires weighing the benefits and potential risks to the HIV-infected woman and her child despite numerous uncertainties. Further research is a high priority and should include a) clarification of long-term risks of the ZDV regimen to the woman and/or her child, b) elucidation of the reasons for transmission despite use of

the ZDV regimen, c) delineation of the relative efficacy of the various components of the ACTG Protocol 076 ZDV regimen for reducing transmission, d) evaluation of the efficacy of the regimen in women whose characteristics differ from those enrolled in ACTG Protocol 076, and e) evaluation of other interventions for preventing perinatal transmission. As further information becomes available, these recommendations may need to be modified. In addition, appropriate methods and materials should be developed for communicating treatment options, risks, and benefits to women and health-care providers so that they can make informed decisions about treatment.

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BOX 3. Summary: Clinical situations and recommendations for use of zidovudine* to reduce perinatal HIV transmission

I. Pregnant HIV-infected women with CD4+ T-lymphocyte counts ≥200/μL who are at 14–34 weeks of gestation and who have no clinical indications for ZDV and no history of extensive (>6 months) prior antiretroviral therapy.

Recommendation:
The health-care provider should recommend the full ACTG Protocol 076 regimen to all HIV-infected pregnant women in this category. This recommendation should be presented to the pregnant woman in the context of a risk-benefit discussion: a reduced risk of transmission can be expected, but the long-term adverse consequences of the regimen are not known. The decision about this regimen should be made by the woman after discussion with her health-care provider.

II. Pregnant HIV-infected women who are at >34 weeks of gestation, who have no history of extensive (>6 months) prior antiretroviral therapy, and who do not require ZDV for their own health.

Recommendation:
The health-care provider should recommend the full ACTG Protocol 076 regimen in the context of a risk-benefit discussion with the pregnant woman. The woman should be informed that ZDV therapy may be less effective than that observed in ACTG Protocol 076, because the regimen is being initiated late in the third trimester.

III. Pregnant HIV-infected women with CD4+ T-lymphocyte counts <200/μL who are at 14–34 weeks of gestation, who have no other clinical indications for ZDV, and who have no history of extensive (>6 months) prior antiretroviral therapy.

Recommendation:
The health-care provider should recommend initiation of antenatal ZDV therapy to the woman for her own health benefit. The intrapartum and neonatal components of the ACTG Protocol 076 regimen should be recommended until further information becomes available. This recommendation should be presented in the context of a risk-benefit discussion with the pregnant woman.

IV. Pregnant HIV-infected women who have a history of extensive (>6 months) ZDV therapy and/or other antiretroviral therapy before pregnancy.

Recommendation:
Because data are insufficient to extrapolate the potential efficacy of the ACTG Protocol 076 regimen for this population of women, the health-care provider should consider recommending the ACTG Protocol 076 regimen

*These recommendations do not represent approval by the Food and Drug Administration (FDA) or approved labeling for the particular product or indications in question.

BOX 3. Summary: Clinical situations and recommendations for use of zidovudine to reduce perinatal HIV transmission (Continued)

on a case-by-case basis after a discussion of the risks and benefits with the pregnant woman. Issues to be discussed include her clinical and immunologic stability on ZDV therapy, the likelihood she is infected with a ZDV-resistant HIV strain, and, if relevant, the reasons for her current use of an alternative antiretroviral agent (e.g., lack of response to or intolerance of ZDV therapy). Consultation with experts in HIV infection may be warranted. The health-care provider should make the ACTG Protocol 076 regimen available to the woman, although its effectiveness may vary depending on her clinical status.

V. Pregnant HIV-infected women who have not received antepartum antiretroviral therapy and who are in labor.

Recommendation:
For women with HIV infection who are in labor and who have not received the antepartum component of the ACTG Protocol 076 regimen (either because of lack of prenatal care or because they did not wish to receive antepartum therapy), the health-care provider should discuss the benefits and potential risks of the intrapartum and neonatal components of the ACTG Protocol 076 regimen and offer ZDV therapy when the clinical situation permits.

VI. Infants who are born to HIV-infected women who have received no intrapartum ZDV therapy.

Recommendation:
If the clinical situation permits and if ZDV therapy can be initiated within 24 hours of birth, the health-care provider should offer the ACTG Protocol 076 postpartum component of 6 weeks of neonatal ZDV therapy for the infant in the context of a risk-benefit discussion with the mother. Data from animal prophylaxis studies indicate that, if ZDV is administered, therapy should be initiated as soon as possible (within hours) after delivery. If therapy cannot begin until the infant is >24 hours of age and the mother did not receive therapy during labor, no data support offering therapy to the infant.

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MORBIDITY AND MORTALITY WEEKLY REPORT

Update: Trends in AIDS Incidence, Deaths, and Prevalence — United States, 1996

The national acquired immunodeficiency syndrome (AIDS) surveillance system is used to describe the impact of HIV-related morbidity and death in the United States. This report presents trends in AIDS incidence during 1996 and describes recent declines in deaths among persons reported with AIDS (AIDS deaths) and increases in AIDS prevalence.*

Cumulative AIDS cases among persons aged ≥13 years reported to CDC based on the 1993 expanded surveillance case definition from the 50 states, the District of Columbia, Puerto Rico, and the U.S. territories were analyzed by year of report, race/ethnicity, and mode of risk/exposure (*1*). Estimates of AIDS incidence and deaths were adjusted for the effects of delays in reporting. For analyses by mode of risk/exposure, estimates were adjusted for the anticipated reclassification of cases initially reported without an HIV risk/exposure (*1*). To adjust for the expansion of the reporting criteria in 1993, estimates of the incidence of AIDS-opportunistic illnesses (OIs) were calculated from the sum of cases diagnosed with an AIDS-OI and the estimated dates of an AIDS-OI diagnosis for cases reported based on immunologic criteria† (*1*). AIDS-OI incidence was estimated quarterly through June 1996, the most recent period for which reliable estimates were available. Estimates of AIDS-OI incidence rates per 100,000 population were based on 1995 population estimates from the Bureau of the Census. Deaths among persons with AIDS were identified by review of medical records and death certificates and include both deaths from AIDS and from other causes. AIDS prevalence was estimated from cumulative AIDS incidence minus cumulative deaths.

Reported AIDS Cases

From 1981 through 1996, a total of 573,800 persons aged ≥13 years with AIDS were reported to CDC by state and local health departments (Table 1). The expansion of the AIDS surveillance case definition in 1993 resulted in a large increase in reported cases

*Single copies of this report will be available until February 28, 1998, from the CDC National AIDS Clearinghouse, P.O. Box 6003, Rockville, MD 20849-6003; telephone (800) 458-5231 or (301) 217-0023.

†The immunologic criteria that were added to the AIDS case definition in 1993 were CD4+ T-lymphocyte count <200 cells/μL or CD4+ T-lymphocyte percentage of total lymphocytes of <14.

TABLE 1. Number and percentage of persons aged ≥13 years reported with AIDS, by sex and race/ethnicity — United States, 1981–1996

	Year of report											
	1992		1993*		1994		1995		1996		1981–1996	
Characteristic	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**
Sex												
Male	40,330	(86)	87,945	(84)	64,730	(82)	59,285	(81)	54,653	(80)	488,300	(85)
Female	6,307	(14)	16,671	(16)	13,830	(18)	13,682	(19)	13,820	(20)	85,500	(15)
Race/Ethnicity												
White, non-Hispanic	22,320	(48)	47,468	(45)	32,677	(42)	29,402	(40)	26,229	(38)	267,487	(47)
Black, non-Hispanic	15,576	(33)	37,523	(36)	30,373	(39)	28,729	(39)	28,346	(41)	198,780	(35)
Hispanic	8,223	(18)	18,410	(18)	14,612	(19)	13,961	(19)	12,966	(19)	101,253	(18)
Asian/Pacific Islander	334	(<1)	761	(<1)	573	(<1)	558	(<1)	561	(<1)	4,090	(<1)
American Indian/ Alaskan Native	121	(<1)	369	(<1)	246	(<1)	237	(<1)	207	(<1)	1,544	(<1)
Total†	**46,637**	**(100)**	**104,616**	**(100)**	**78,560**	**(100)**	**72,967**	**(100)**	**68,473**	**(100)**	**573,800**	**(100)**

*Year the expanded AIDS surveillance case definition was implemented.
†Totals inlcude persons with unknown or missing race/ethnicity.

AIDS — Continued

during 1993 followed by declines in numbers of AIDS cases reported each year from 1994 through 1996. The 68,473 AIDS cases reported during 1996 was substantially higher (47%) than the number reported during 1992.

From 1992 through 1996, non-Hispanic blacks, Hispanics, and women accounted for increasing proportions of persons reported with AIDS. In 1996, non-Hispanic blacks accounted for 41% of adults reported with AIDS, exceeding for the first time the proportion who were non-Hispanic white, and women accounted for an all-time high of 20% of adults reported with AIDS.

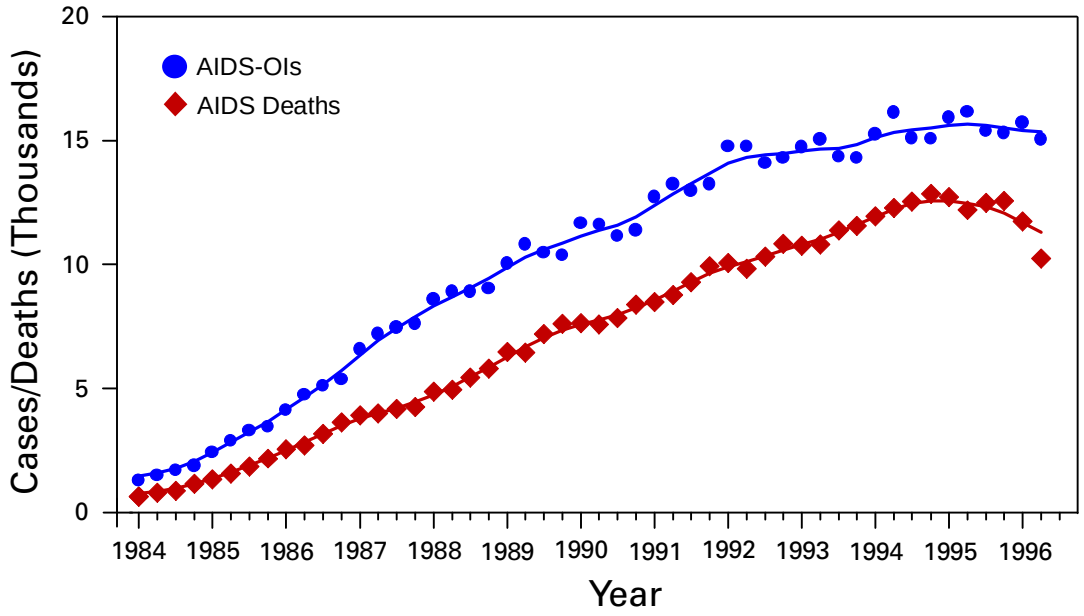
AIDS-OI Incidence

In 1995, AIDS-OIs were diagnosed in an estimated 62,200 persons, an increase of 2% over the estimate for 1994 (61,200) (Figure 1). From January 1994 through June 1996, the quarterly incidence of AIDS-OIs was stable (mean: 15,200 cases per quarter).

During 1995, estimated AIDS-OI incidence rates per 100,000 population were approximately sevenfold higher among non-Hispanic blacks (99) and threefold higher among Hispanics (50) than among non-Hispanic whites (15). Estimated rates were lowest among American Indians/Alaskan Natives (14) and Asians/Pacific Islanders (6) and were nearly five-fold greater among men (48) than among women (10).

From 1994 through 1995, estimated AIDS-OI incidence was approximately constant (a decrease of 2%) among men who have sex with men (MSM) (Figure 2) and among heterosexual injecting-drug users (IDUs) (an increase of 2%) (Figure 3), but increased substantially among persons infected through heterosexual contact (17%) (Figure 4).

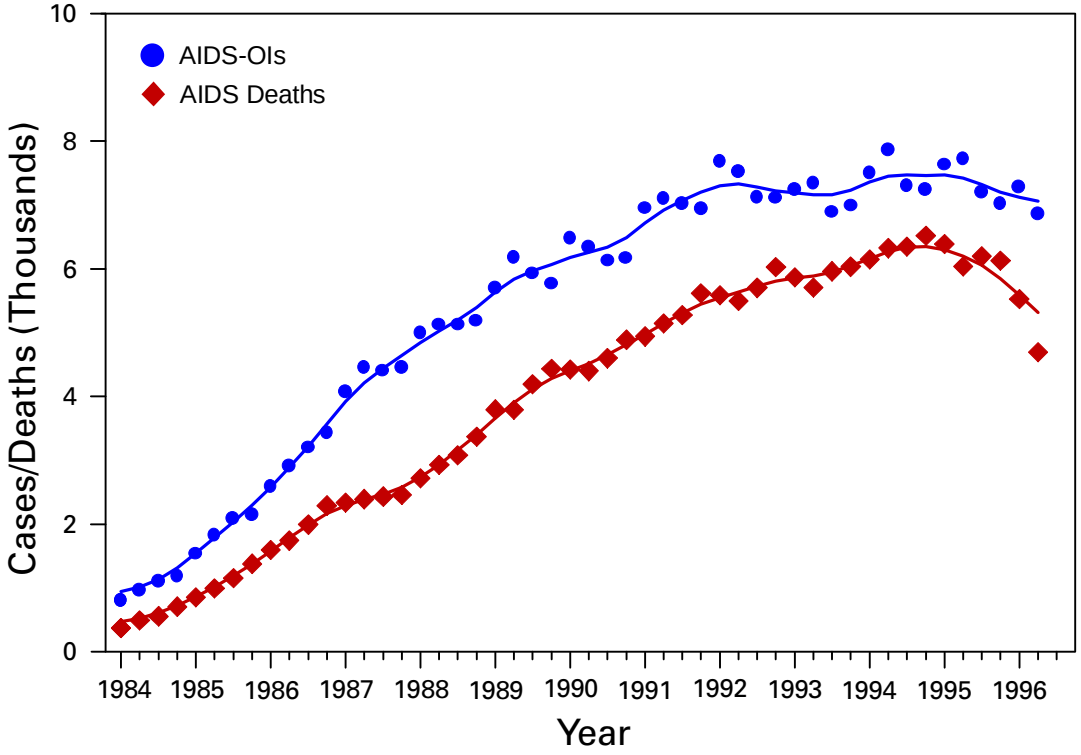
FIGURE 1. Estimated AIDS-opportunistic illness (OI) incidence and estimated deaths among persons with AIDS (AIDS deaths)*, adjusted for delays in reporting, by quarter year of diagnosis/death — United States, 1984–June 1996†



*Estimates include persons aged <13 years.
†Points represent quarterly incidence; lines represent "smoothed" incidence. Estimates are not adjusted for incomplete reporting of diagnosed AIDS cases.

AIDS — Continued

FIGURE 2. Estimated AIDS-opportunistic illness (OI) incidence and estimated deaths among persons aged ≥13 years with AIDS (AIDS deaths), by exposure category (men who have sex with men), adjusted for delays in reporting, by quarter year of diagnosis/death — United States, 1984–June 1996*



*Points represent quarterly incidence; lines represent "smoothed" incidence. Estimates are not adjusted for incomplete reporting of diagnosed AIDS cases.

Of the 30,100 persons in whom AIDS-OIs were diagnosed during January–June 1996, 46% were MSM, 29% were IDUs, and 17% were infected through heterosexual contact.

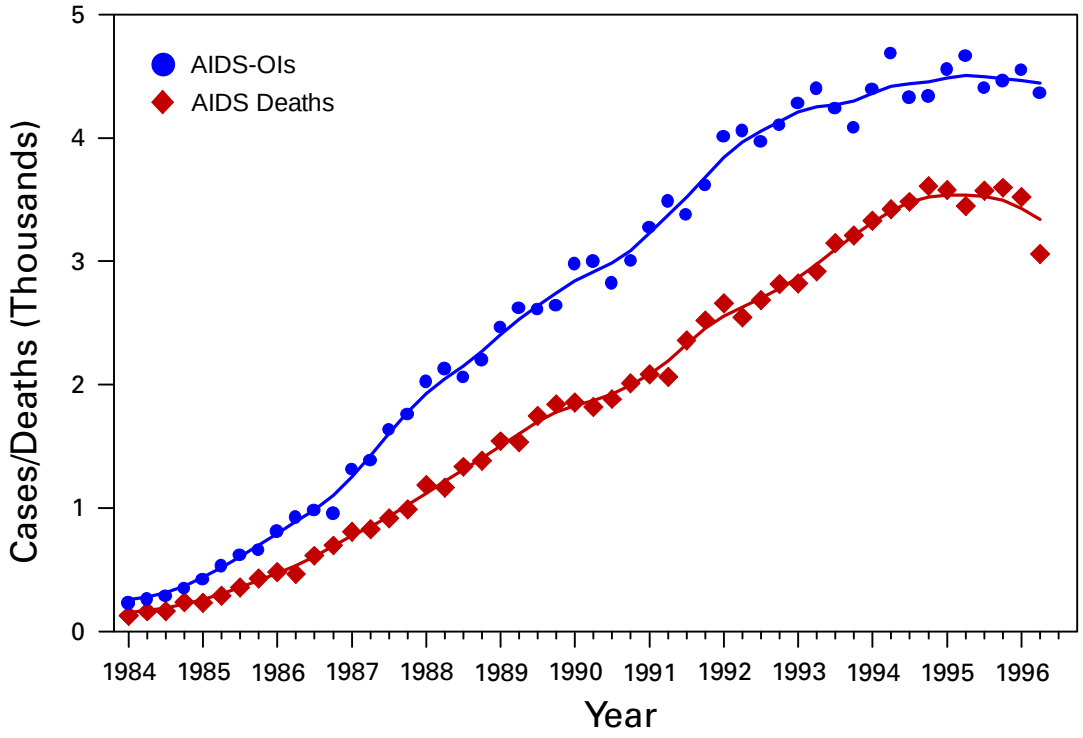
Deaths Among Persons Reported with AIDS

The estimated number of deaths among persons reported with AIDS increased steadily through 1994 (approximately 49,600 deaths among persons with AIDS during 1994) (Figure 1) but increased only slightly in 1995 (approximately 50,000 deaths). During January–June 1996, the estimated number of AIDS deaths (22,000) was 13% less than that estimated during January–June 1995 (24,900), and the number of deaths declined in each of the four regions of the United States (Northeast [15%], South [8%], Midwest [11%], and West [16%])[§]. The number of AIDS deaths also declined among all racial/ethnic groups (non-Hispanic whites [21%], non-Hispanic blacks [2%], Hispanics [10%], Asians/Pacific Islanders [6%], and American Indians/Alaskan Natives [32%])

[§]Northeast=Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont; Midwest=Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin; South=Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia; and West=Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming.

AIDS — Continued

FIGURE 3. Estimated AIDS-opportunistic illness (OI) incidence and estimated deaths among persons aged ≥13 years with AIDS (AIDS deaths), by exposure category (injecting-drug use), adjusted for delays in reporting, by quarter year of diagnosis/death — United States, 1984–June 1996*



*Points represent quarterly incidence; lines represent "smoothed" incidence. Estimates are not adjusted for incomplete reporting of diagnosed AIDS cases.

and among men (15%) but increased 3% among women. By risk/exposure category, deaths declined 18% among MSM (Figure 2) and 6% among IDUs (Figure 3) but increased 3% among persons infected through heterosexual contact (Figure 4), the only risk/exposure group with large increases in AIDS-OI incidence during 1995.

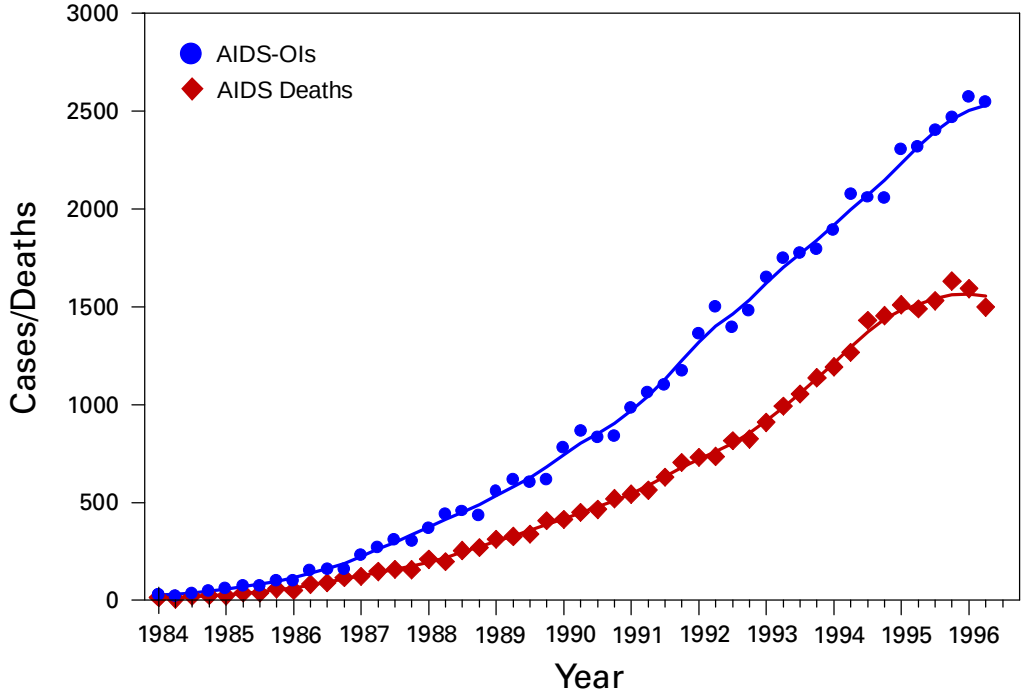
AIDS Prevalence

As of June 1996, the estimated prevalence of AIDS was 223,000 U.S. residents aged ≥13 years (Figure 5), representing increases of 10% and 65% since mid-1995 and January 1993, respectively. Of prevalent cases of AIDS, 82% were among men; 43%, non-Hispanic whites; 38%, non-Hispanic blacks; and 19%, Hispanics. By risk/exposure category, MSM accounted for the largest number of prevalent cases of AIDS (44%), followed by IDUs (26%) and persons infected through heterosexual contact (12%); all other risk/exposure groups¶ combined accounted for 18% of prevalent cases of AIDS. The largest proportionate increase in AIDS prevalence from June 1995 through June 1996 occurred among persons infected through heterosexual contact (19%) while the largest absolute increase occurred among MSM (5100).

¶Includes men who reported both having sex with men and injecting-drug use, persons with hemophilia/coagulation disorders, transfusion recipients, and persons with other or no risks reported.

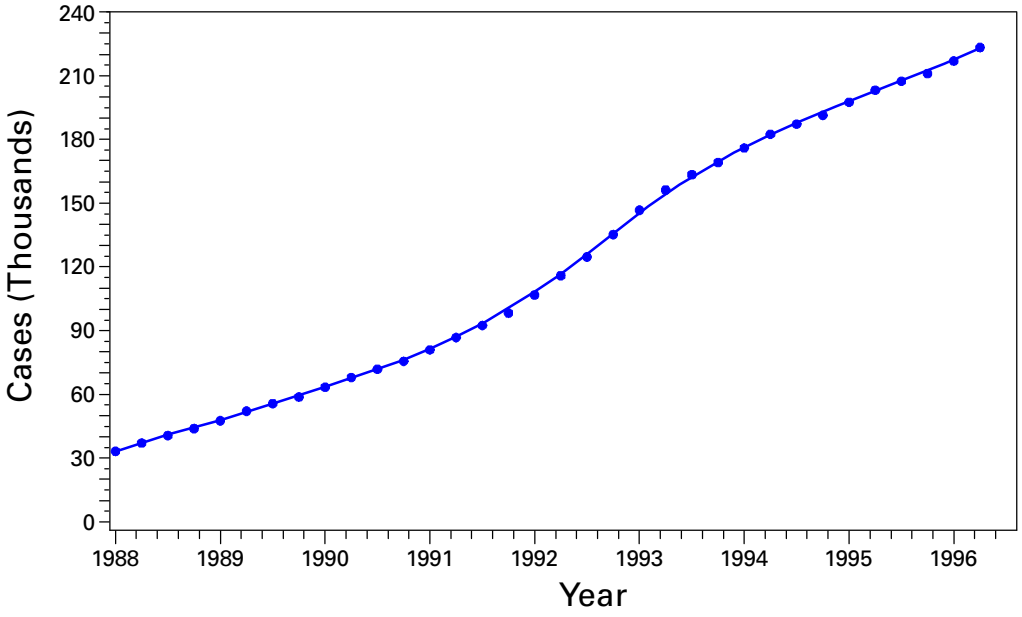
AIDS — Continued

FIGURE 4. Estimated AIDS-opportunistic illness (OI) incidence and estimated deaths among persons aged ≥13 years with AIDS (AIDS deaths), by exposure category (HIV infection acquired through heterosexual contact), adjusted for delays in reporting, by quarter year of diagnosis/death — United States, 1984–June 1996*



*Points represent quarterly incidence; lines represent "smoothed" incidence. Estimates are not adjusted for incomplete reporting of diagnosed AIDS cases.

FIGURE 5. Number of prevalent AIDS cases among persons aged ≥13 years, adjusted for delays in reporting, by quarter year — United States, 1988–June 1996*



*Points represent quarterly prevalence; the line represents "smoothed" prevalence. Estimates are not adjusted for incomplete reporting of diagnosed AIDS cases or AIDS deaths.

AIDS — Continued

Reported by: State and local health depts. Div of HIV/AIDS Prevention—Surveillance and Epidemiology, National Center for HIV, STD, and TB Prevention, CDC.

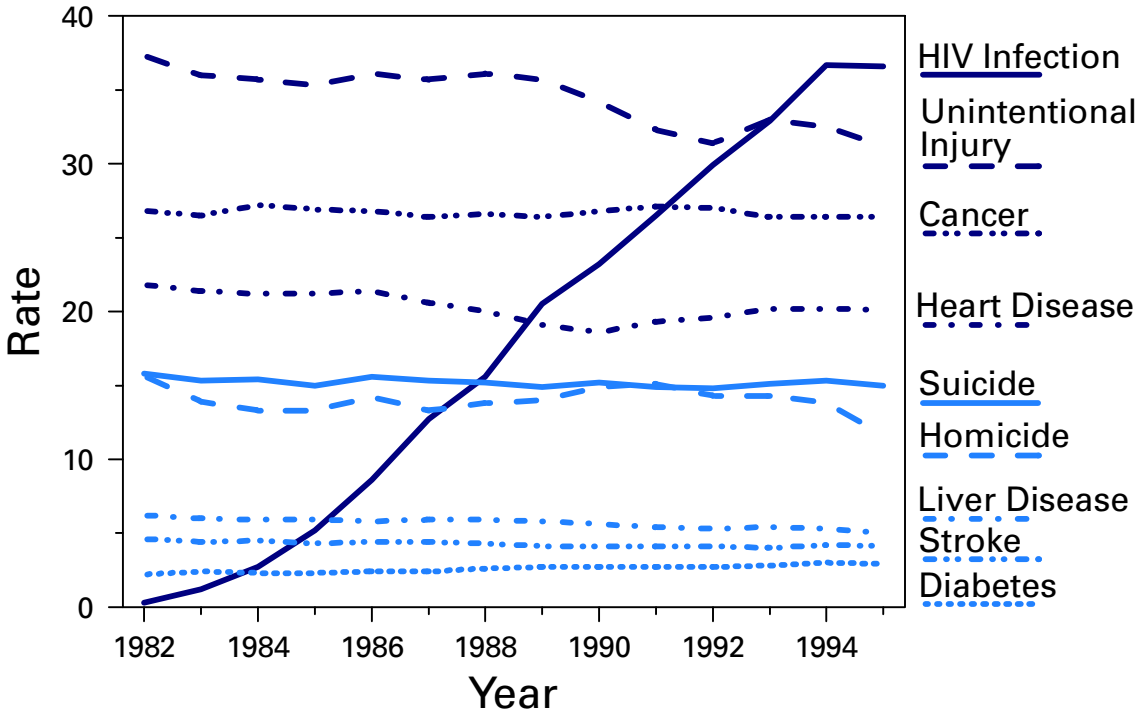
Editorial Note: The findings in this report document a substantial increase in AIDS prevalence in the United States. Prevalence is a function of both the rate of new infections and the duration of illness. The increase in AIDS prevalence reflects declines in AIDS deaths and stable AIDS incidence. The increased prevalence of AIDS indicates the need for medical and other services for persons with HIV infection and for prevention programs to reduce the number of persons becoming infected with HIV.

The leveling of AIDS-OI incidence nationally in 1995 was preceded by a gradual deceleration in the rate of increase of new AIDS diagnoses during previous years (*1*). Similar trends have been documented among MSM and IDUs in clinic-based HIV-seroprevalence surveys (*2*). However, the incidence of cases associated with heterosexual contact has continued to increase, primarily reflecting transmission from the large population of IDUs with HIV/AIDS to their heterosexual partners.

For the first time, deaths among persons with AIDS have decreased substantially. This finding is consistent with recent reports, based on death-certificate data, of declines in deaths from HIV infection in New York City (*3*) and nationally (*4*). Despite these trends, during 1995 HIV infection remained the leading cause of death among persons aged 25–44 years (Figure 6), accounting for 19% of deaths from all causes in this age group.

The decrease in AIDS deaths reflects both the leveling of AIDS-OI incidence and improved survival among persons with AIDS. Increased survival reflects recent im-

FIGURE 6. Death rates* for leading causes of death among persons aged 25–44 years, by year — United States, 1982–1995†



*Per 100,000 population.
†Based on underlying cause of death reported on death certificates, using final data for 1982–1994 and preliminary data for 1995.

AIDS — Continued

provements in medical care, the use of combination therapy with antiretroviral agents, and increasing use of prophylactic drugs to prevent secondary AIDS-OIs (*5*). In addition, the widespread availability of protease inhibitors, approved by the Food and Drug Administration in 1996, may further improve survival (*6*).

The higher AIDS-OI incidence rates among non-Hispanic blacks and Hispanics than among non-Hispanic whites may reflect reduced access to health care associated with disadvantaged socioeconomic status, cultural or language barriers that may limit access to prevention information, and differences in HIV risk behaviors (*7*). The number of AIDS deaths did not decrease among women or persons infected through heterosexual contact, reflecting, in part, continued increases in AIDS incidence and differences in access to treatment, which may vary by sex, region, race/ethnicity, and risk/exposure. To assist prevention efforts and treatment services, surveillance systems are being developed to assess access to counseling, testing, and care.

Monitoring AIDS prevalence will help direct resources to persons most in need of treatment for severe HIV disease. However, because the clinical status of most HIV-infected persons has not yet progressed to AIDS (*8*), AIDS prevalence underestimates the total number of HIV-infected persons in need of related services. Advances in treatment and improved survival also will affect efforts to monitor the HIV epidemic based on the current AIDS surveillance definition and, therefore, will require surveillance systems that are less sensitive to changes in the progression of HIV disease. Among the 26 states that conducted surveillance for cases of both HIV infection and AIDS in 1996, prevalence of HIV and AIDS among reported cases (126,491) was 2.5-fold higher than the prevalence of AIDS (51,217) (*1*). However, this represents a minimum estimate of HIV prevalence in these states because not all HIV-infected persons seek testing and some persons are tested anonymously.

The Council of State and Territorial Epidemiologists has recommended that all states consider implementing surveillance for HIV infection and AIDS (*9*). Population-based surveillance for both HIV and AIDS provides a more complete measure of the number of HIV-infected persons and a more timely measure to detect emerging patterns of HIV transmission than does AIDS surveillance alone. CDC provides technical assistance and funding to areas that conduct both HIV and AIDS case surveillance. CDC also supports research to develop optimal surveillance methods that meet the need for important behavioral, biomedical, and treatment data for persons with HIV and AIDS and that address public health and community concerns about factors that may influence decision-making regarding testing or treatment.

Future trends in the HIV/AIDS epidemic in the United States will reflect the effectiveness of programs to prevent new HIV infections, to promote timely diagnosis, and to continue improving clinical management. CDC has established as a primary prevention strategy efforts to involve affected communities in planning and evaluating HIV-prevention programs (*10*). To continue to provide data for planning, directing, and evaluating HIV prevention and care services at the federal, state, and local levels, HIV/AIDS surveillance systems must adapt to changes in the diagnosis and clinical management of HIV and AIDS.

AIDS — Continued

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Update: Influenza Activity — United States, 1996–97 Season

Influenza activity in the United States has continued to decline since mid-January 1997. The predominant viruses have been influenza type A (H3N2), although the proportion of influenza B isolates has increased since the week ending January 18. This report summarizes influenza activity in the United States from September 29, 1996, through the week ending February 15, 1997.

The proportion of patients who visited 120 U.S. sentinel physicians for influenza-like illness (ILI) peaked at 7% from mid-December through the first week of January and was 3% of total visits by the week ending February 15, 1997. The proportion of visits for ILI had remained at or below the baseline level of 3% since the week ending January 25, 1997; however, the proportion of ILI visits had not yet reached baseline levels in the West South Central and Pacific regions through the week ending February 15, 1997.

Influenza activity* has decreased since the week ending December 28, 1996, when state and territorial epidemiologists in 38 states reported either widespread or regional activity. For the week ending February 15, 1997, either widespread or regional influenza activity was reported in 21 states and sporadic activity was reported in 25 states and the District of Columbia (Figure 1). None of the states in the East North Central region reported regional or widespread activity for the week ending February 15.

*Levels of activity are 1) *no activity*; 2) *sporadic*—sporadically occurring ILI or culture-confirmed influenza with no outbreaks detected; 3) *regional*—outbreaks of ILI or culture-confirmed influenza in counties with a combined population of <50% of the state's total population; and 4) *widespread*—outbreaks of ILI or culture-confirmed influenza in counties with a combined population of ≥50% of the state's total population.

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Recommendations and Reports

MORBIDITY AND MORTALITY WEEKLY REPORT

Report of the NIH Panel to Define Principles of Therapy of HIV Infection

and

Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Preface

The past 2 years have witnessed remarkable advances in the development of antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infection, as well as measurement of HIV plasma RNA (viral load) to guide the use of antiretroviral drugs. The use of ART, in conjunction with the prevention of specific HIV-related opportunistic infections (OIs), has been associated with dramatic decreases in the incidence of OIs, hospitalizations, and deaths among HIV-infected persons.

Advances in this field have been so rapid, however, that keeping up with them has posed a formidable challenge to health-care providers and to patients, as well as to institutions charged with the responsibility of paying for these therapies. Thus, the Office of AIDS Research, the National Institutes of Health, and the Department of Health and Human Services, in collaboration with the Henry J. Kaiser Foundation, have assumed a leadership role in formulating the scientific principles (NIH Panel) and developing the guidelines (DHHS/Kaiser Panel) for the use of antiretroviral drugs that are presented in this report. CDC staff participated in these efforts, and CDC and *MMWR* are pleased to be able to provide this information as a service to its readers.

This report is targeted primarily to providers who care for HIV-infected persons, but it also is intended for patients, payors, pharmacists, and public health officials. The report comprises two articles. The first article, *Report of the NIH Panel To Define Principles of Therapy of HIV Infection,* provides the basis for the use of antiretroviral drugs, and the second article, *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents,* provides specific recommendations regarding when to start, how to monitor, and when to change therapy, as well as specific combinations of drugs that should be considered. Both articles provide cross-references to each other so readers can locate related information. Tables and figures are included in the Appendices section that follows each article. Although the principles are unlikely to change in the near future, the guidelines will change substantially as new information and new drugs become available.

Copies of this document and all updates are available from the CDC National AIDS Clearinghouse (1-800-458-5231) and are posted on the Clearinghouse World-Wide Web site (http://www.cdcnac.org). In addition, copies and updates also are available from the HIV/AIDS Treatment Information Service (1-800-448-0440; Fax 301-519-6616; TTY 1-800-243-7012) and on the ATIS World-Wide Web site (http://www.hivatis.org). Readers should consult these web sites regularly for updates in the guidelines.

Report of the NIH Panel To Define Principles of Therapy of HIV Infection

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Report of the NIH Panel To Define Principles of Therapy of HIV Infection*

Summary

Recent research advances have afforded substantially improved understanding of the biology of human immunodeficiency virus (HIV) infection and the pathogenesis of the acquired immunodeficiency syndrome (AIDS). With the advent of sensitive tools for monitoring HIV replication in infected persons, the risk of disease progression and death can be assessed accurately and the efficacy of anti-HIV therapies can be determined directly. Furthermore, when used appropriately, combinations of newly available, potent antiviral therapies can effect prolonged suppression of detectable levels of HIV replication and circumvent the inherent tendency of HIV to generate drug-resistant viral variants. However, as antiretroviral therapy for HIV infection has become increasingly effective, it has also become increasingly complex. Familiarity with recent research advances is needed to ensure that newly available therapies are used in ways that most effectively improve the health and prolong the lives of HIV-infected persons. To enable practitioners and HIV-infected persons to best use rapidly accumulating new information about HIV disease pathogenesis and treatment, the Office of AIDS Research of the National Institutes of Health sponsored the NIH Panel to Define Principles of Therapy of HIV Infection. This Panel was asked to define essential scientific principles that should be used to guide the most effective use of antiretroviral therapies and viral load testing in clinical practice. Based on detailed consideration of the most current data, the Panel delineated eleven principles that address issues of fundamental importance for the treatment of HIV infection. These principles provide the scientific basis for the specific treatment recommendations made by the Panel on Clinical Practices for the Treatment of HIV Infection sponsored by the Department of Health and Human Services and the Henry J. Kaiser Family Foundation. The reports of both of these panels are provided in this publication. Together, they summarize new dta and provide both the scientific basis and specific guidelines for the treatment of HIV-infected persons. This information will be of interest to health-care providers, HIV-infected persons, HIV/AIDS educators, public health educators, public health authorities, and all organizations that fund medical care of HIV-infected persons.

INTRODUCTION

The past 2 years have brought major advances in both basic and clinical research on acquired immunodeficiency syndrome (AIDS). The availability of more numerous and more potent drugs to inhibit human immunodeficiency virus (HIV) replication has made it possible to design therapeutic strategies involving combinations of antiretroviral drugs that accomplish prolonged and near complete suppression of

*Information included in these principles may not represent FDA approval or approved labeling for the particular products or indications in question. Specifically, the terms "safe" and "effective" may not be synonymous with the FDA-defined legal standards for product approval.

detectable HIV replication in many HIV-infected persons. In addition, more sensitive and reliable measurements of plasma viral load have been demonstrated to be powerful predictors of a person's risk for progression to AIDS and time to death. They have also been demonstrated to reliably assess the antiviral activity of therapeutic agents.

It is now critical that these scientific advances be translated into information that practitioners and their patients can utilize in making decisions about using the new therapies and monitoring tools to achieve the greatest, most durable clinical benefits. Such information will allow physicians to tailor more effective treatments for their patients and to more closely monitor patients' responses to specific antiretroviral regimens.

A two-track process was initiated to address this pressing need. The Office of AIDS Research of the National Institutes of Health (NIH) sponsored the NIH Panel To Define Principles of Therapy of HIV Infection. This Panel was asked to delineate the scientific principles, based on its understanding of the biology and pathogenesis of HIV infection and disease, that should be used to guide the most effective use of antiretroviral therapy and viral load testing in clinical practice.

The Department of Health and Human Services (HHS) and the Henry J. Kaiser Family Foundation sponsored the Panel on Clinical Practices for the Treatment of HIV Infection. The HHS Panel was charged with developing recommendations, based on the scientific principles, for the clinical use of antiretroviral drugs and laboratory monitoring methods in the treatment of HIV-infected persons. Both documents—the *Report of the NIH Panel To Define Principles of Therapy for HIV Infection*, developed by the NIH Panel, and the *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*, developed by the HHS Panel—are provided in this report.

Together, these two documents summarize new data and provide both the scientific basis and specific guidelines for the treatment of HIV-infected persons. The goal of this report is to assist clinicians and patients in making informed decisions about treatment options so that a) effective antiretroviral therapy is introduced before extensive immune system damage has occurred; b) viral load monitoring is used as an essential tool in determining an HIV-infected person's risk for disease progression and response to antiretroviral therapy; c) combinations of antiretroviral drugs are used to suppress HIV replication to below the limits of detection of sensitive viral load assays; and d) patient adherence to the complicated regimens of combination antiretroviral therapy that are currently required to achieve durable suppression of HIV replication is encouraged by patient–provider relationships that provide education and support concerning the goals, strategies, and requirements of antiretroviral therapy.

The NIH Panel included clinicians, basic and clinical researchers, public health officials, and community representatives. As part of its effort to accumulate the most current data, the Panel held a 2-day public meeting to hear presentations by clinicians and scientists in the areas of HIV pathogenesis and treatment, specifically addressing the following topics: the relationship between virus replication and disease progression; the relative ability of available strategies of antiviral therapy to minimize HIV replication for prolonged periods of time; the relationship between the emergence of drug resistance and treatment failures; the relative ability of available strategies of antiviral therapy to delay or prevent the emergence of drug-resistant HIV variants; and the relationship between drug-induced changes in virus load and improved clinical outcomes and prolonged survival.

Summary of the Principles of Therapy of HIV Infection

1. Ongoing HIV replication leads to immune system damage and progression to AIDS. HIV infection is always harmful, and true long-term survival free of clinically significant immune dysfunction is unusual.
2. Plasma HIV RNA levels indicate the magnitude of HIV replication and its associated rate of CD4+ T cell destruction, whereas CD4+ T cell counts indicate the extent of HIV-induced immune damage already suffered. Regular, periodic measurement of plasma HIV RNA levels and CD4+ T cell counts is necessary to determine the risk for disease progression in an HIV-infected person and to determine when to initiate or modify antiretroviral treatment regimens.
3. As rates of disease progression differ among HIV-infected persons, treatment decisions should be individualized by level of risk indicated by plasma HIV RNA levels and CD4+ T cell counts.
4. The use of potent combination antiretroviral therapy to suppress HIV replication to below the levels of detection of sensitive plasma HIV RNA assays limits the potential for selection of antiretroviral-resistant HIV variants, the major factor limiting the ability of antiretroviral drugs to inhibit virus replication and delay disease progression. Therefore, maximum achievable suppression of HIV replication should be the goal of therapy.
5. The most effective means to accomplish durable suppression of HIV replication is the simultaneous initiation of combinations of effective anti-HIV drugs with which the patient has not been previously treated and that are not cross-resistant with antiretroviral agents with which the patient has been treated previously.
6. Each of the antiretroviral drugs used in combination therapy regimens should always be used according to optimum schedules and dosages.
7. The available effective antiretroviral drugs are limited in number and mechanism of action, and cross-resistance between specific drugs has been documented. Therefore, any change in antiretroviral therapy increases future therapeutic constraints.
8. Women should receive optimal antiretroviral therapy regardless of pregnancy status.
9. The same principles of antiretroviral therapy apply to HIV-infected children, adolescents, and adults, although the treatment of HIV-infected children involves unique pharmacologic, virologic, and immunologic considerations.
10. Persons identified during acute primary HIV infection should be treated with combination antiretroviral therapy to suppress virus replication to levels below the limit of detection of sensitive plasma HIV RNA assays.
11. HIV-infected persons, even those whose viral loads are below detectable limits, should be considered infectious. Therefore, they should be counseled to avoid sexual and drug-use behaviors that are associated with either transmission or acquisition of HIV and other infectious pathogens.

These topics and other data assessed by the Panel in formulating the scientific principles were derived from three primary sources: recent basic insights into the life cycle of HIV, studies of the extent and consequences of HIV replication in infected persons, and clinical trials of anti-HIV drugs.

In certain instances, the Panel based the principles and associated corollaries on clinical studies conducted in relatively small numbers of patients for fairly short periods of time. After carefully evaluating data from these studies, the Panel concluded that the results of several important contemporary studies have been consistent in their validation of recent models of HIV pathogenesis.

The Panel believes that new antiretroviral drugs and treatment strategies, if used correctly, can substantially benefit HIV-infected persons. However, as the understanding of HIV disease has improved and the number of available beneficial therapies has increased, clinical care of HIV-infected patients has become much more complex. Therapeutic success increasingly depends on a thorough understanding of the pathogenesis of HIV disease and on familiarity with when and how to use the more numerous and more effective drugs available to treat HIV infection. The Panel is concerned that even these new potent antiretroviral therapies will be of little clinical utility for treated patients unless they are used correctly and that, used incorrectly, they may even compromise the potential to obtain long-term benefit from other antiretroviral therapies in the future.

The principles and conclusions discussed in this report have been developed and made available now so that practitioners and patients can make treatment decisions based on the most current research results. Undoubtedly, insights into the pathogenesis of HIV disease will continue to accumulate rapidly, providing new targets for the development of additional antiretroviral drugs and even more effective treatment strategies. Thus, the Panel expects that these principles will require modification and elaboration as new information is acquired.

SCIENTIFIC PRINCIPLES

Principle 1. Ongoing HIV replication leads to immune system damage and progression to AIDS. HIV infection is always harmful, and true long-term survival free of clinically significant immune dysfunction is unusual.

Active replication of HIV is the cause of progressive immune system damage in infected persons (*1–10*). In the absence of effective inhibition of HIV replication by antiretroviral therapy, nearly all infected persons will suffer progressive deterioration of immune function resulting in their susceptibility to opportunistic infections (OIs), malignancies, neurologic diseases, and wasting, ultimately leading to death (*11,12*).

For adults who live in developed countries, the average time of progression to AIDS after initial infection is approximately 10–11 years in the absence of antiretroviral therapy or with older regimens of nucleoside analog (e.g., zidovudine [ZDV]) monotherapy (*11*). Some persons develop AIDS within 5 years of infection (20%), whereas others (<5%) have sustained long-term (>10 years) asymptomatic HIV infection without decline of CD4+ T cell counts to <500cells/mm^3. Only approximately 2% or less of HIV-infected persons seem to be able to contain HIV replication to extremely low levels and maintain stable CD4+ T cell counts within the normal range for lengthy

periods (>12 years), and many of these persons display laboratory evidence of immune system damage (*12*). Thus, HIV infection is unusual among human virus infections in causing disease in such a large proportion of infected persons.

Although a very small number of HIV-infected persons do not demonstrate progressive HIV disease in the absence of antiretroviral therapy, there is no definitive way to prospectively identify these persons. Therefore, all persons who have HIV infection must be considered at risk for progressive disease. The goals of treatment for HIV infection should be to maintain immune function in as near a normal state as possible, prevent disease progression, prolong survival, and preserve quality of life by effectively suppressing HIV replication. For these goals to be accomplished, therapy should be initiated, whenever possible, before extensive immune system damage has occurred.

Principle 2. Plasma HIV RNA levels indicate the magnitude of HIV replication and its associated rate of CD4+ T cell destruction, whereas CD4+ T cell counts indicate the extent of HIV-induced immune damage already suffered. Regular, periodic measurement of plasma HIV RNA levels and CD4+ T cell counts is necessary to determine the risk for disease progression in an HIV-infected person and to determine when to initiate or modify antiretroviral treatment regimens.

The rate of progression of HIV disease is predicted by the magnitude of active HIV replication (reflected by so-called viral load) taking place in an infected person (*5–10,13–18*). Measurement of viral load through the use of quantitative plasma HIV RNA assays permits assessment of the relative risk for disease progression and time to death (*5-10,13–18*). Plasma HIV RNA measurements also permit assessment of the efficacy of antiretroviral therapies in individual patients (*1,2,13,19–25*). It is expert opinion that these measurements are necessary components of treatment strategies designed to use antiretroviral drugs most effectively. The extent of immune system damage that has already occurred in an HIV-infected person is indicated by the CD4+ T cell count (*11,26–29*), which permits assessment of the risk for developing specific OIs and other sequelae of HIV infection. When used in concert with viral load determinations, assessment of CD4+ T cell number enhances the accuracy with which the risk for disease progression and death can be predicted (*27*). Issues specific for the laboratory assessment of plasma HIV RNA and CD4+ T cell levels in HIV-infected infants and young children are discussed in Principle 9 (*14–18,25,30*). Important specific considerations regarding laboratory evaluations and HIV-infected persons include the following:

1. In the newly diagnosed patient, baseline plasma HIV RNA levels should be checked in a clinically stable state. Plasma HIV RNA levels obtained within the first 6 months of initial HIV infection do not accurately predict a person's risk for disease progression (*31*). In contrast, plasma HIV RNA levels stabilize (reach a "set-point") after approximately 6–9 months of initial HIV infection and are then predictive of risk for disease progression (*5–10*). Following their stabilization, plasma HIV RNA levels may remain fairly stable for months to years in many HIV-infected persons (*7,10*). However, immunizations and intercurrent infections can lead to transient elevations of plasma HIV RNA levels (*32–34*). As a result, values obtained within approximately 4 weeks of such episodes may not accurately reflect a person's actual baseline plasma HIV RNA level. For an accu-

rate baseline, two specimens obtained within 1–2 weeks of each other, processed according to optimal, validated procedures, and analyzed by the same quantitative method are recommended. The use of two baseline measurements serves to reduce the variance in the plasma HIV RNA assays that results from technical and biologic factors (*19,22,35,36*).

2. Studies of populations of HIV-infected persons indicate that plasma HIV RNA levels gradually increase with time after infection (*10*). A steeper rate of increase is associated with an increased risk of disease progression. Within individual patients, the actual rate of change of plasma HIV RNA levels is unpredictable but can increase abruptly. Therefore, periodic monitoring of plasma HIV RNA levels is necessary to accurately gauge risk of disease progression. (See Guidelines.)
3. Studies of the kinetics of HIV replication in infected persons indicate that levels of plasma HIV RNA should measurably decline within days of initiation of effective combination antiretroviral therapy (*1,2,20,21,37*). In patients in whom cessation of detectable new rounds of HIV infection of CD4+ T cells occurs, plasma HIV RNA levels should fall to approximately 1% of their initial levels within 2 weeks after initiation of therapy, reaching a nadir (ideally below the limit of detection of sensitive plasma HIV RNA assays) within approximately 8 weeks. Persons who have very high initial plasma HIV RNA levels may take longer to reach a nadir of plasma RNA levels following initiation of effective antiretroviral therapy (up to approximately 16 weeks). (See Guidelines.)
4. Plasma HIV RNA assays provide the best measure of the activity of antiretroviral therapy of HIV-infected persons. Rebound of plasma HIV RNA levels following their suppression by antiretroviral therapy may indicate the outgrowth of drug-resistant HIV variants in a patient adherent to the regimen (see Principle 7 for additional considerations). Should the desired level of suppression of HIV replication be accomplished in treated patients by 16 weeks after initiation or alteration of an antiretroviral regimen, plasma HIV RNA levels should be checked periodically to document the continued activity of the chosen antiretroviral regimen.
5. HIV RNA levels can vary by approximately threefold (0.5 $\log_{10}$) in either direction, upon repeated measurements (obtained withing days or weeks of each other) in clinically stable, HIV-infected persons (*19,22,35,36*). Changes greater than 0.5 $\log_{10}$ usually cannot be explained by inherent biological or assay variability and likely reflect a biologically and clinically relevant change in the level of plasma HIV RNA. It is important to note that the variability of the current plasma HIV RNA assays is greater toward their lower limits of sensitivity. Thus, differences between repeated measures of greater than 0.5 $\log_{10}$ may be seen at very low plasma HIV RNA values and may not reflect a substantive biological or clinical change.
6. CD4+ T cell counts should be obtained for all patients who have newly diagnosed HIV infection (*28,29*) (See Guidelines).
7. CD4+ T cell counts are subject to substantial variability due to both biological and laboratory methodologies (*26*) and can vary up to 30% on repeated measures in the absence of a change in clinical status. Thus, it is important to monitor trends over time rather than base treatment decisions on one specific determination.

8. In patients who are not receiving antiretroviral therapy, CD4+ T cell counts should be checked regularly to monitor patients for evidence of disease progression. (See Guidelines.)
9. In patients receiving antiretroviral therapy, CD4+ T cell counts should be checked regularly to document continuing immunologic benefit and to assess the current degree of immunodeficiency (*28,29*). (See Guidelines.)
10. It is not yet known whether a given CD4+ T cell level achieved in response to antiretroviral therapy provides an equivalent assessment of the degree of immune system function or has the same predictive value for risk for OIs as do CD4+ T cell levels obtained in the absence of therapy. The potentially incomplete recovery of T cell function and the diversity of antigen recognition, despite CD4+ T cell increases induced by antiretroviral therapy, have raised concerns that patients may remain susceptible to OIs at higher CD4+ T cell levels. Until more data concerning this issue are available, the Panel concurs with recent U.S. Public Health Service/Infectious Diseases Society of America recommendations that prophylactic medications be continued when CD4+ T cell counts increase above recommended threshold levels as a result of initiation of effective antiretroviral therapies (i.e., that the provision of prophylaxis be based on the lowest reliably determined CD4+ T cell count) (*28*).
11. Measurements of p24 antigen, neopterin, and β-2 microglobulin levels have often been used to assess risk for disease progression. However, these measurements are less reliable than plasma HIV RNA assays and do not add clinically useful prognostic information to that obtained from HIV RNA and CD4+ T cell levels. As such, these laboratory tests need not be included as part of the routine care of HIV-infected patients.

Principle 3. As rates of disease progression differ among HIV-infected persons, treatment decisions should be individualized by level of risk indicated by plasma HIV RNA levels and CD4+ T cell counts.

Decisions regarding when to initiate antiretroviral therapy in an HIV-infected person should be based on the risk for disease progression and degree of immunodeficiency. Initiation of antiretroviral therapy before the onset of immunologic and virologic evidence of disease progression is expected to have the greatest and most durable beneficial impact on preserving the health of HIV-infected persons. When specific viral load or CD4+ T cell levels at which therapy should be initiated are considered, it is important to recognize that the risk for disease progression is a continuous rather than discrete function (*5,6,10,27*). There is no known absolute threshold of HIV replication below which disease progression will not eventually occur. At present, recommendations for initiation of therapy must be based on the fact that the types and numbers of available antiretroviral drugs are limited. When more numerous, more effective, better tolerated, and more conveniently dosed drugs become available, it is likely that indications for initiation of therapy will change accordingly. Specific considerations regarding treatment include the following:

1. Decisions made by health-care practitioners and HIV-infected patients regarding initiation of antiretroviral therapy should be guided by the patient's plasma HIV RNA level and CD4+ T cell count. (See Guidelines.)

2. Data are not yet available that define the degree of therapeutic benefit in persons who have relatively high CD4+ T cell counts and relatively low plasma HIV RNA levels (e.g., CD4+ T cell count >500/mm^3 and plasma HIV RNA <10,000 copies/mL). However, emerging insights into the pathogenesis of HIV disease predict that antiretroviral therapy should be of benefit to such patients. For persons at low risk for disease progression, decisions concerning when to initiate antiretroviral therapy must also include consideration of the potential inconvenience and toxicities of the available antiretroviral drugs. Should the decision be made to defer therapy, regular monitoring of HIV RNA levels and CD4+ T cell counts should be performed as recommended (See Guidelines).
3. Persons who have levels of HIV RNA persistently below the level of detection of currently available HIV RNA assays and who have stable, high CD4+ T cell counts in the absence of therapy are at low risk for disease progression in the near future. The potential for benefit of treatment for these persons is not known. Should the decision be made to defer therapy, regular monitoring of HIV RNA levels and CD4+ T cell counts should be performed as recommended (see Guidelines).
4. Patients who have late-stage disease (as indicated by clinical evidence of advanced immunodeficiency or low CD4+ T cell counts, e.g., <50 cells/mm^3) have benefited from appropriate antiretroviral therapy as evidenced by decreased risks for further disease progression or death (*23,28*). In such patients, antiretroviral therapy can be of benefit even when CD4+ T cell increases are not seen. Therefore, discontinuation of antiretroviral therapy in this setting should be considered only if available antiretroviral therapies do not suppress HIV replication to a measurable degree, if drug toxicities outweigh the anticipated clinical benefit, or if survival and quality of life are not expected to be improved by antiretroviral therapy (e.g., terminally ill persons).

Principle 4. The use of potent combination antiretroviral therapy to suppress HIV replication to below the levels of detection of sensitive plasma HIV RNA assays limits the potential for selection of antiretroviral-resistant HIV variants, the major factor limiting the ability of antiretroviral drugs to inhibit virus replication and delay disease progression. Therefore, maximum achievable suppression of HIV replication should be the goal of therapy.

Studies of the biology and pathogenesis of HIV infection have provided the basis for using antiretroviral drugs in ways that yield the most profound and durable suppression of HIV replication. The inherent ability of HIV to develop drug resistance represents the major obstacle to the long-term efficacy of antiretroviral therapy (*21*). However, recent clinical evidence indicates that the development of drug resistance can be delayed, and perhaps even prevented, by the rational use of combinations of drugs that include newly available, potent agents to suppress HIV replication to levels that cannot be detected by sensitive assays of plasma HIV RNA (*23,38–40*). Cessation of detectable HIV replication decreases the opportunity for accumulation of mutations that may give rise to drug-resistant viral variants. Furthermore, the extent and duration of inhibition of HIV replication by antiretroviral therapy predicts the magnitude of clinical benefit derived from treatment (*9,13,23–25*).

The potential toxicities of therapy, as well as the patient's quality of life and ability to adhere to a complex antiretroviral drug regimen, should be balanced with the anticipated clinical benefit of maximal suppression of HIV replication and the anticipated risks of less complete suppression. Specific considerations regarding treatment include the following:

1. Once a decision has been made to initiate antiretroviral therapy, the ideal goal of therapy should be suppression of the level of active HIV replication, as assessed by sensitive measures of plasma HIV RNA, to undetectable levels.
2. If suppression of HIV replication to undetectable levels cannot be achieved, the goal of therapy should be to suppress virus replication as much as possible for as long as possible. Less complete suppression of HIV replication is expected to yield less profound and less durable immunologic and clinical benefits. Higher residual levels of HIV replication during therapy predispose the patient to more rapid development of antiretroviral drug resistance and associated waning of clinical benefit. In the absence of effective suppression of detectable HIV replication, it is currently impossible to identify a precise target level for suppression of HIV replication that will yield predictable clinical benefits. However, recent data indicate that suppression of HIV RNA levels to <5,000 copies/mL is likely to yield more greater and more durable clinical benefit than less complete suppression (*24*).
3. The HIV RNA assays currently available have similar levels of sensitivity (*19,41–46* ; Table). More sensitive versions of each of these assays are currently in development and will likely be commercially available in the future. Once these assays are available, the goal of antiretroviral therapy should be suppression of HIV RNA levels to below detection of these more sensitive assays. Less profound suppression of HIV replication is associated with a greater likelihood of development of drug resistance (*23,40*).
4. Although suppression of HIV load to levels below the detection limits of sensitive plasma HIV RNA assays indicates profound inhibition of new cycles of virus replication, it does not mean that the infection has been eradicated or that virus replication has been stopped completely (*37,47–50*). HIV replication may be continuing in various tissues (e.g., the lymphatic tissues and the central nervous system) although it can no longer be detected by plasma HIV RNA assays. Strategies for potential eradication are being pursued in experimental studies, but the likelihood of their success is uncertain (*37,51*). Recent studies indicate that infectious HIV can still be isolated from CD4+ T cells obtained from infected persons whose plasma HIV RNA levels have been suppressed below detection for prolonged periods (up to 30 months) (*49,50*). Long-term persistence of HIV infection in such persons who have undetectable levels of plasma HIV RNA appears to be due to the existence of long-lived reservoirs of latently infected CD4+ cells, rather than drug failure (*49,50*). Continued monitoring of HIV RNA levels is necessary in patients who have achieved antiretroviral drug-induced suppression of HIV RNA to undetectable levels, as this effect may be transient. (See Guidelines.)

Principle 5. The most effective means to accomplish durable suppression of HIV replication is the simultaneous initiation of combinations of effective anti-HIV drugs with which the patient has not been previously treated and that are not cross-resistant with antiretroviral agents with which the patient has been previously treated.

Several issues should be considered regarding the combination of antiretroviral drugs to be used in the treatment of an HIV-infected patient. The efficacy of a given regimen of combination antiretroviral therapy is not simply a function of the number of drugs used. The most effective antiretroviral drugs possess high potency, favorable pharmacologic properties, and require that HIV acquire multiple mutations in the relevant HIV target gene before high-level drug resistance is realized. In addition, drug-resistant HIV variants selected for by treatment with certain antiretroviral drugs may display diminished ability to replicate (decreased "fitness") in infected persons (*21*). Drugs used in combination should show evidence of additivity or synergy of antiretroviral activity, should lack antagonistic pharmacokinetic or antiretroviral properties, and should possess nonoverlapping toxicities. Ideally, the chosen drugs will display molecular interactions that increase the potency of antiretroviral therapy or delay the emergence of antiretroviral drug resistance. If multiple options are available for combination therapy, specific antiretroviral drugs should be employed so that future therapeutic options are preserved if the initial choice of therapy fails to achieve its desired result. Whenever possible, therapy should be initiated or modified with a rational combination of antiretroviral drugs, a predefined target for the degree of suppression of HIV replication desired, and a predefined alternative antiretroviral regimen to be used should the target goal not be reached. Specific considerations regarding treatment include the following:

1. The combination of antiretroviral drugs used when therapy is either initiated or changed needs to be carefully chosen because it will influence subsequent options for effective antiretroviral therapy if the chosen drug regimen fails to accomplish satisfactory suppression of HIV replication.
2. The best opportunity to accomplish maximal suppression of virus replication, minimize the risk of outgrowth of drug-resistant HIV variants, and maximize protection from continuing immune system damage is to use combinations of effective antiretroviral drugs in persons who have no prior history of anti-HIV therapy.
3. No single antiretroviral drug that is currently available, even the more potent protease inhibitors (PIs), can ensure sufficient and durable suppression of HIV replication when used as a single agent ("monotherapy"). Furthermore, the use of potent antiretroviral drugs as single agents presents a great risk for the development of drug resistance and the potential development of cross-resistance to related drugs. Thus, antiretroviral monotherapy is no longer a recommended option for treatment of HIV-infected persons (see Guidelines). One exception is the use of zidovudine (ZDV) according to the AIDS Clinical Trials Group (ACTG) 076 regimen. This regimen is specifically for the purpose of reducing the risk for perinatal HIV transmission in pregnant women who have high CD4+ T cell counts and low plasma HIV RNA levels and who have not yet decided to initiate antiretroviral therapy based on their own health indications (*52–54*). This time-limited use of zidovudine by a pregnant woman to prevent perinatal HIV trans-

mission has important benefits to infants and is not likely to substantially compromise her future ability to benefit from combination antiretroviral therapy.

4. Antiretroviral drugs (e.g., lamivudine [3TC]) or the non-nucleoside reverse transcriptase inhibitors (NNRTIs; e.g., nevirapine and delavirdine), that are potent, but to which HIV readily develops high-level resistance, should not be used in regimens that are expected to yield incomplete suppression of detectable HIV replication.
5. At present, durable suppression of detectable levels of HIV replication is best accomplished with the use of two nucleoside analog reverse transcriptase (RT) inhibitors combined with a potent PI. In patients who have not been treated with antiretroviral therapy, suppression of detectable HIV replication has also been reported with the use of two nucleoside analog RT inhibitors combined with a NNRTI (e.g., zidovudine, didanosine, and nevirapine [*40*]). However, the role of this approach as initial antiretroviral therapy needs to be better defined before it can be recommended as a "first-line" treatment strategy. Furthermore, this approach is considerably less effective in persons who have been previously treated with nucleoside analog RT inhibitors (*55–57*). In the subset of previously treated patients who respond initially to such regimens, suppression of HIV replication is often transient and the associated clinical benefit is limited.
6. The use of fewer than three antiretroviral drugs in combination may be considered as an option by HIV-infected persons and their physicians. In making this decision, it is important to recognize that no combination of two currently available nucleoside analog RT inhibitors has been demonstrated to consistently provide sufficient and durable suppression of HIV replication. Although the initial decline in HIV RNA levels following treatment with two RT inhibitors may be encouraging, the durability of the response beyond 24–48 weeks in controlled studies has been disappointing (*40,56–60*). Furthermore, the selection of drug-resistant HIV variants by antiretroviral regimens that fail to suppress HIV replication durably may compromise the range of future treatment options. Even in antiretroviral-drug–naive patients, the use of NNTRIs is not routinely recommended in combination with one nucleoside analog RT inhibitor, as the risk for selection of NNRTI-resistant HIV variants is high in regimens that fail to achieve suppression of detectable HIV replication (*1,61*). Certain combinations of two protease inhibitors (without added RT inhibitors) have been reported to provide suppression of detectable HIV replication in pilot studies (*62,63*); however, given the limited experience available with this approach, it should not be considered as a first-line regimen at the present time. (See Guidelines.)
7. When a change in therapy is considered in a previously treated patient, a review of the person's prior history of anti-HIV therapy is essential. Drugs chosen as the components of a new antiretroviral regimen should not be cross-resistant to previously used antiretroviral drugs (or share similar patterns of mutations associated with antiretroviral drug resistance). (See Principle 7 for additional considerations.)
8. When changing a failing regimen, it is important to change more than one component of the regimen. The addition of single antiretroviral agents, even very potent ones, is likely to lead to the development of viral resistance to the new agent. (See Guidelines.)

Principle 6. Each of the antiretroviral drugs used in combination therapy regimens should always be used according to optimum schedules and dosages.

The use of combinations of potent antiretroviral drugs to exert constant, maximal suppression of HIV replication provides the best approach to circumvent the inherent tendency of HIV to generate drug-resistant variants. Specific considerations regarding treatment include the following:

1. Combination therapy should be initiated with all drugs started simultaneously (ideally within 1 or 2 days of each other); antiretroviral therapies should not be added sequentially. Staged introduction of individual antiretroviral drugs increases the likelihood that incomplete suppression of HIV replication will be achieved, thereby permitting the progressive accumulation of mutations that confer resistance to multiple antiretroviral agents. Rather than strive to increase patient acceptance of therapy through the sequential addition of antiretroviral drugs, the Panel believes it is better to counsel and educate patients extensively before the initiation of antiretroviral therapy, even if it means a limited delay in initiating treatment.
2. Whenever possible, combination antiretroviral therapy should be maintained at recommended drug doses. At any time after initiation of therapy, underdosing with any one agent in a combination, or the administration of fewer than all drugs of a combination at any one time, should be avoided. Antiretroviral drug resistance is less likely to occur if *all* antiretroviral therapy is temporarily stopped than if the dosage of one or more components is reduced or if one component of an effective suppressive regimen is withheld. Should antiretroviral drug resistance develop as a result of underdosing or irregular dosing of antiretroviral drugs, subsequent readministration of recommended doses of drugs on a regular schedule is unlikely to accomplish effective suppression of HIV replication.
3. Patient adherence to an antiretroviral regimen is critical to the success of therapy. If antiretroviral drugs are used in inadequate doses or are used only intermittently, the risk for developing drug-resistant HIV variants is greatly increased. Effective adherence to complicated medical regimens requires extensive patient education about the goals and rationale for therapy before it is initiated, as well as an ongoing, active collaboration between practitioner and patient when therapy has been started. Counseling should include careful review of the drug-dosing intervals, the possibility of co-administration of several medications at the same time, and the relationship of drug dosing to meals and snacks.
4. Available effective regimens of combination antiretroviral therapy require that patients take multiple medications at specific times of the day. Persons who have unstable living situations or limited social support mechanisms may have difficulty adhering to the recommended antiretroviral therapy regimens and may need special support from health-care workers to do so effectively. If circumstances impede adherence to the most effective antiretroviral regimens now available, therapy is unlikely to be of long-term benefit to the patient and the risk of selection of drug-resistant HIV variants is increased. Therefore, it is important to ensure that adequate social support is available for patients who are offered combination antiretroviral therapy. Health-care providers should work with HIV-infected patients to assess if they are ready and able to commit to

a regimen of antiviral therapy. Health-care providers should make such assessment on an individual basis and not consider that any specific group of persons are unable to adhere.

Principle 7. The available effective drugs are limited in number and mechanism of action, and cross-resistance between specific drugs has been documented. Therefore, any change in antiretroviral therapy increases future therapeutic constraints.

Decisions to alter therapy will rely heavily on consideration of clinical issues and on the number of available alternative antiretroviral agents. Every decision made to alter therapy may limit future treatment options. Thus, available agents should not be abandoned prematurely. It is not known definitively whether the pathogenic consequences of a measurable level of HIV replication while on therapy are equivalent to those of an equivalent level in an untreated person; however, preliminary data suggest that this is the case. Thus, the level at which HIV replication continues while on an antiretroviral drug regimen that has failed to suppress plasma HIV RNA to below detectable levels should be considered as an indication of the urgency with which an alteration in therapy should be pursued. Specific considerations regarding treatment include the following:

1. Increasing levels of plasma HIV RNA in a person receiving antiretroviral therapy can be caused by several factors. Identification of the responsible factor, wherever possible, is an important goal. Evidence of increased levels of HIV replication may signal the emergence of drug-resistant HIV variants, incomplete adherence to the antiretroviral therapy, decreased absorption of antiretroviral drugs, altered drug metabolism due to physiologic changes or drug-drug interactions, or intercurrent infection.
2. Before the decision is made to alter antiretroviral therapy because of an increase in plasma HIV RNA, it is important to repeat the plasma HIV RNA measurements to avoid unnecessary changes based on misleading or spurious plasma HIV RNA values (e.g., the presence of intercurrent infection or imperfect adherence to therapy).
3. Antiretroviral therapy should be changed when plasma HIV RNA again becomes detectable (repeatedly and in the absence of events such as imperfect adherence to the regimen, immunizations, or intercurrent infections that may lead to transient elevations of plasma HIV RNA levels) and continues to rise in a patient in whom it had been previously suppressed to undetectable levels. In a person whose plasma HIV RNA levels had been previously incompletely suppressed, progressively increasing plasma HIV RNA levels should prompt consideration of a change in antiretroviral therapy. (See Guidelines.)
4. Evidence of antiretroviral drug toxicity or intolerance is also an important reason to consider changes in drug therapy. In certain instances, these manifestations may be transient, and therapy may be safely continued with attention to patient counseling and continuing evaluation. When it is necessary to change therapy for reasons of toxicity or intolerance, alternative antiretroviral drugs should be chosen based on their anticipated efficacy and lack of similar toxicities. In this situation, substitution of one drug (ideally of the same class and possessing equal or greater antiretroviral activity) for another, while continuing the other components of the regimen, is reasonable.

Principle 8. Women should receive optimal antiretroviral therapy regardless of pregnancy status.

The use of antiretroviral treatment in HIV-infected pregnant women raises important, unique concerns (*64*). HIV counseling and the offer of HIV testing to pregnant women have been universally recommended in the United States and are now mandatory in some states. A greater awareness of issues surrounding HIV infection in pregnant women has resulted in an increased number of women whose initial diagnosis of HIV infection is made during pregnancy. In this circumstance, or when women already aware of their HIV infection become pregnant, treatment decisions should be based on the current and future health of the mother, as well as on preventing perinatal transmission and ensuring the health of the fetus and neonate. Care of the HIV-infected pregnant woman should involve a collaboration between the HIV specialist caring for the woman when she is not pregnant, her obstetrician, and the woman herself. Treatment recommendations for HIV-infected pregnant women are based on the belief that therapies of known benefit to women should not be withheld during pregnancy unless there are known adverse effects on the mother, fetus, or infant that outweigh the potential benefit to the woman (*64*). There are two separate but interconnected issues regarding antiretroviral treatment during pregnancy: a) use of antiretroviral therapy for maternal health indications and b) use of antiretroviral drugs for reducing the risk of perinatal HIV transmission. Although zidovudine monotherapy substantially reduces the risk of perinatal HIV transmission, appropriate combinations of antiretroviral drugs should be administered if indicated on the basis of the mother's health. In general, pregnancy should not compromise optimal HIV therapy for the mother. Specific considerations regarding treatment of pregnant women include the following:

1. Recommendations regarding the choice of antiretroviral agents in pregnant women are subject to unique considerations, including potential changes in dose requirements due to physiologic changes associated with pregnancy and potential effects of the drug on the fetus and neonate (e.g., placental passage of drug and preclinical data indicating potential for teratogenicity, mutagenicity, or carcinogenicity). (See Guidelines.)
2. No long-term safety studies are available regarding the use of any antiretroviral agents during pregnancy. Because the first trimester of pregnancy (i.e., weeks 1–14) is the most vulnerable time with respect to teratogenicity (particularly the first 8 weeks), it may be advisable to delay, when feasible, the initiation of antiretroviral therapy until 14 weeks' gestational age. However, if clinical, virologic, or immunologic parameters are such that therapy would be recommended for nonpregnant persons, many experts would recommend initiating therapy, regardless of gestational age.
3. Women who are already receiving antiretroviral therapy at the time that pregnancy is diagnosed should continue their therapy. Alternatively, if pregnancy is anticipated or discovered early in the first trimester (before 8 weeks), concern for potential teratogenicity may lead some women to consider stopping antiretroviral therapy until 14 weeks' gestation. Although the effects of all antiretroviral drugs on the developing fetus during the first trimester are uncertain, most experts recommend continuation of a maximally suppressive regimen even during the first trimester. Currently, insufficient data exist to support or refute concerns

about potential teratogenicity. If antiretroviral therapy is discontinued for any reason during the first trimester, all agents should be discontinued simultaneously. Once they are reinstituted, they should be reintroduced simultaneously.

4. Treatment of a pregnant woman with an antiretroviral regimen that does not suppress HIV replication to below detectable levels is likely to result in the development of antiretroviral drug-resistant HIV variants and limit her ability to respond favorably to effective combination therapy regimens in the future. The emergence of drug-resistant HIV variants during incomplete suppression of HIV replication in a pregnant woman may limit the ability of those same antiretroviral drugs to effectively decrease the risk of perinatal transmission if provided intrapartum and/or to the neonate.
5. Transmission of HIV from mother to infant can occur at all levels of maternal viral loads, although higher viral loads tend to be associated with an increased risk of transmission (*53,65*). Zidovudine therapy is effective at reducing the risk for perinatal HIV transmission regardless of maternal viral load (*53,54*). Therefore, use of the recommended regimen of zidovudine alone or in combination with other antiretroviral drugs should be discussed with and offered to all HIV-infected pregnant women, regardless of their plasma HIV RNA level (*54*).

Principle 9. The same principles of antiretroviral therapy apply to HIV-infected children, adolescents, and adults, although the treatment of HIV-infected children involves unique pharmacologic, virologic, and immunologic considerations.

Most of the data that support the principles of antiretroviral therapy outlined in this document have been generated in studies of HIV-infected adults. Adolescents infected with HIV sexually or through drug use appear to follow a clinical course similar to adults, and recommendations for antiretroviral therapy for these persons are the same as for adults (see Guidelines). However, although fewer data are available concerning treatment of HIV infection in younger persons, it is unlikely that the fundamental principles of HIV disease differ for HIV-infected children. Furthermore, the data that are available from studies of HIV-infected infants and children indicate that the same fundamental virologic principles apply, and optimal treatment approaches are also likely to be similar (*14–18,25*). Therefore, HIV-infected children, as previously described for HIV-infected adults, should be treated with effective combinations of antiretroviral drugs with the intent of accomplishing durable suppression of detectable levels of HIV replication.

Unfortunately, not all of the antiretroviral drugs that have demonstrated efficacy in combination therapy regimens in adults are available in formulations (e.g., palatable liquid formulations) for infants and young children (particularly for those aged <2 years). In addition, pharmacokinetic and pharmacodynamic studies of some antiretroviral agents have yet to be completed in children. Thus, effective antiretroviral therapies should be studied in children and age-specific pharmacologic properties of these therapies should be defined. Antiretroviral drugs selected to treat HIV-infected children should be used only if their pharmacologic properties have been defined in the relevant age group of the patient. Use of antiretroviral drugs before these properties have been defined may result in undesirable toxicities without virologic or clinical benefit.

Identification of HIV-infected infants soon after delivery or during the first few weeks following their birth provides opportunities for treatment of primary HIV infection and, perhaps, for facilitating the most effective treatment responses (*16–18,66*). Thus, identification of HIV-infected women through voluntary testing, provision of antiretroviral therapy to the mother and infant to decrease the risk of maternal-infant transmission, and careful screening of infants born to HIV-infected mothers for evidence of HIV infection will provide an effective strategy to ameliorate the risk and consequences of perinatal HIV infection.

The specific HIV RNA and CD4+ T cell criteria used for making decisions about when to initiate therapy in infected adults do not apply directly to newborns, infants, and young children (*14–18*). As with adults, higher levels of plasma HIV RNA are associated with a greater risk of disease progression and death in infants and young children (*14–18*). However, absolute levels of plasma HIV RNA observed during the first years of life in HIV-infected children are frequently higher than those found in adults infected for similar lengths of time, and establishment of a post-primary–infection set-point takes substantially longer in infected children (*15–18*). The increased susceptibility of children to OIs, particularly *Pneumocystis carinii* pneumonia (PCP), at higher CD4+ T cell counts than HIV-infected adults (*30*) further indicates that the CD4+ T cell criteria suggested as guides for initiation of antiretroviral therapy in HIV-infected adults are not appropriate to guide therapeutic decisions for infected children. In all, the need for and potential benefits of early institution of effective antiretroviral therapy are likely to be even greater in children than adults, suggesting that most, if not all, HIV-infected children should be treated with effective combination antiretroviral therapies.

Principle 10. Persons identified during acute primary HIV infection should be treated with combination antiretroviral therapy to suppress virus replication to levels below the limit of detection of sensitive plasma HIV RNA assays.

Studies of HIV pathogenesis provide theoretical support for the benefits of antiretroviral therapy for persons diagnosed with primary HIV infection, and data that are accumulating from small-scale clinical studies are consistent with these predictions (*49,66–73*). Results from studies suggest that antiretroviral therapy during primary infection may preserve immune system function by blunting the high level of HIV replication and immune system damage occurring during this period and potentially reducing set-point levels of HIV replication, thereby favorably altering the subsequent clinical course of the infection; however, this outcome has yet to be formally demonstrated (*51,73*). It has been further suggested that the best opportunity to eradicate HIV infection might be provided by the initiation of potent combination antiretroviral therapy during primary infection (*51*).

The Panel believes that, although the long-term benefits of effective combination antiretroviral therapy of primary infection are not known, it is a critical topic of investigation. Therefore, enrollment of newly diagnosed patients in clinical trials should be encouraged to help in defining the optimal approach to treatment of primary infection. When this is neither feasible nor desired, the Panel believes that combination antiretroviral therapy with the goal of suppression of HIV replication to undetectable levels should be pursued. The Panel believes that suppressive antiretroviral therapy

for acute primary HIV infection should be continued indefinitely until clinical trials provide data to establish the appropriate duration of therapy.

Principle 11. HIV-infected persons, even those whose viral loads are below detectable limits. Therefore, they should be considered infectious. Therefore, they should be counseled to avoid sexual and drug-use behaviors that are associated with either transmission or acquisition of HIV and other infectious pathogens.

No data are available concerning the ability of HIV-infected persons who have antiretroviral therapy-induced suppression of HIV replication to undetectable levels (assessed by plasma HIV RNA assays) to transmit the infection to others. Similarly, their ability to acquire a multiply resistant HIV variant from another person remains a possibility. HIV-infected persons who are receiving antiretroviral therapy continue to be able to transmit serious infectious diseases to others (e.g., hepatitis B and C and sexually transmitted infections, such as herpes simplex virus, human papillomavirus syphilis, gonorrhea, chancroid, and chlamydia) and are themselves at risk for infection with these pathogens, as well as others that carry serious consequences for immunosuppressed persons, including cytomegalovirus and human herpes virus 8 (also known as KSHV). Therefore, all HIV-infected persons, including those receiving effective antiretroviral therapies, should be counseled to avoid behaviors associated with the transmission of HIV and other infectious agents. Continued reinforcement that all HIV-infected persons adhere to safe-sex practices is important. If an HIV-infected injecting-drug user is unable or unwilling to refrain from using injection drugs, that person should be counseled to avoid sharing injection equipment with others and to use sterile, disposable needles and syringes for each injection.

SCIENTIFIC BACKGROUND

HIV Infection Leads to Progressive Immune System Damage in Nearly All Infected Persons

Early efforts to synthesize a coherent model of the pathogenic consequences of HIV infection were based on the presumption that few cells in infected persons harbor or produce HIV and that virus replication is restricted during the period of clinical latency. However, early virus detection methods were insensitive, and newer, more sensitive tests have demonstrated that virus replication is active throughout the course of the infection and proceeds at levels far higher than previously imagined. HIV replication has been directly linked to the process of T cell destruction and depletion. In addition, ongoing HIV replication in the face of an active but incompletely effective host antiviral immune response is probably responsible for the secondary manifestations of HIV disease, including wasting and dementia.

Beginning with the first cycles of virus replication within the newly infected host, HIV infection results in the progressive destruction of the population of CD4+ T cells that serve essential roles in the generation and maintenance of host immune responses (*1–10*). The target cell preference for HIV infection and depletion is determined by the identity of the cell surface molecule, CD4, that is recognized by the HIV envelope (Env) glycoprotein as the virus binds to and enters host cells to initiate

the virus replication cycle (*74*). Additional cell surface molecules that normally function as receptors for chemokines have recently been identified as essential co-receptors required for the process of HIV entry into target cells (*75*). Macrophages and their counterparts within the central nervous system, the microglial cells, also express cell surface CD4 and provide targets for HIV infection. As macrophages are more resistant to the cytopathic consequences of HIV infection than are CD4+ T cells and are widely distributed throughout the body, they may play critical roles in persistence of HIV infection by providing reservoirs of chronically infected cells.

Although most of the immunologic and virologic assessments of HIV-infected persons have focused on studies of peripheral blood lymphocytes, these cells represent only approximately 2% of the total lymphocyte population in the body. The importance of the lymphoid organs, which contain the majority of CD4+ T cells, has been highlighted by the finding that the concentrations of virus and percentages of HIV-infected CD4+ T cells are substantially higher in lymph nodes (where immune responses are generated and where activated and proliferating CD4+ T cells that are highly susceptible to HIV infection are prevalent) than in peripheral blood (*3,4,48*). Thus, although the depletion of CD4+ T cells after HIV infection is most readily revealed by sampling peripheral blood, damage to the immune system is exacted in lymphoid organs throughout the body (*3,4*). For as yet unidentified reasons, gradual destruction of normal lymph node architecture occurs with time, which probably compromises the ability of an HIV-infected person to generate effective immune responses and replace CD4+ T cells already lost to HIV infection through the expansion of mature T cell populations in peripheral lymphoid tissues. The thymus is also an early target of HIV infection and damage, thereby limiting the continuation of effective T cell production even in younger persons in whom thymic production of CD4+ T cells is active (*76,77*). Thus, in both adults and children, HIV infection compromises both of the potential sources of T cell production, so the rate of T cell replenishment cannot continue indefinitely to match cell loss. Consequently, total CD4+ T cell numbers may decline inexorably in HIV-infected persons.

After initial infection, the pace at which immunodeficiency develops and the attendant susceptibility to OIs which arise are associated with the rate of decline of CD4+ T cell counts (*11,26,27*). The rate at which CD4+ T cell counts decline differs considerably from person to person and is not constant throughout all stages of the infection. Acceleration in the rate of decline of CD4+ T cells heralds the progression of disease. The virologic and immunologic events that occur around this time are poorly understood, but increasing rates of HIV replication, the emergence of viruses demonstrating increased cytopathic effects for CD4+ T cells, and declining host cell-mediated anti-HIV immune responses are often seen (*12,78*). For as yet unknown reasons, host compensatory responses that preserve the homeostasis of total T cell levels (CD4+ plus CD8+ T cells) appear to break down in HIV-infected persons approximately 1–2 years before the development of AIDS, resulting in net loss of total T cells in the peripheral blood, and signaling immune system collapse (*79*).

Although the progression of HIV disease is most readily gauged by declining CD4+ T cell numbers, evidence indicates that the sequential loss of specific types of immune responses also occurs (*80–82*). Memory CD4+ T cells are known to be preferential targets for HIV infection, and early loss of CD4+ memory T cell responses is observed in HIV-infected persons, even before there are substantial decreases in total CD4+ T

cell numbers (*80,81*). With time, gradual attrition of antigen-specific CD4+ T cell-dependent immune recognition may limit the repertoire of immune responses that can be mounted effectively and so predispose the host to infection with opportunistic pathogens (*82*).

HIV Replication Rates in Infected Persons Can Be Accurately Gauged By Measurement of Plasma HIV Concentrations

Until recently, methods for monitoring HIV replication (commonly referred to as viral load) in infected persons were either hampered by poor sensitivity and reproducibility or were so technically laborious that they could not be adapted for routine clinical practice. However, new techniques for sensitive detection and accurate quantification of HIV RNA levels in the plasma of infected persons provide extremely useful measures of active virus replication (*1,2,19,20,37,41–43*). HIV RNA in plasma is contained within circulating virus particles or virions, with each virion containing two copies of HIV genomic RNA. Plasma HIV RNA concentrations can be quantified by either target amplification methods (e.g., quantitative RT polymerase chain reaction [RT-PCR], Amplicor HIV Monitor™ assay, Roche Molecular Systems; or nucleic acid sequence-based amplification, [NASBA®], NucliSens™ HIV-1 QT assay, Organon Teknika) or signal amplification methods (e.g., branched DNA [bDNA], Quantiplex™ HIV RNA bDNA assay, Chiron Diagnostics) (*42,43*). The bDNA signal amplification method (*41*) amplifies the signal obtained from a captured HIV RNA target by using sequential oligonucleotide hybridization steps, whereas the RT-PCR and NASBA® assays use enzymatic methods to amplify the target HIV RNA into measurable amounts of nucleic acid product (41–43). Target HIV RNA sequences are quantitated by comparison with internal or external reference standards, depending upon the assay used. Versions of both types of assays are now commercially available, and the Amplicor assay was recently approved by the Food and Drug Administration for assessment for risk of disease progression and monitoring of antiretroviral therapy in HIV-infected persons. Target amplification assays are more sensitive (400 copies HIV RNA/mL plasma) than the first generation bDNA assay (10,000 copies HIV plasma), but the sensitivity of the bDNA assay has recently been improved (500 copies HIV RNA/mL plasma). More sensitive versions of each of these assays are currently in development (detection limits 20–100 copies/mL) and will likely be commercially available in the future.

All of the commercially available assays can accurately quantitate plasma HIV RNA levels across a wide range of concentrations (so-called dynamic range). Although the results of the three assays (i.e., the RT-PCR, NASBA®, and bDNA) are strongly correlated, the absolute values of HIV RNA measured in the same plasma sample using two different assays can differ by twofold or more (44–46). Until a common standard is available that can be used to normalize values obtained with different assay methods, it is advisable to choose one assay method consistently when HIV RNA levels in infected persons are monitored for use as a guide in making therapeutic decisions.

The performance characteristics and recommended collection methods for the individual HIV RNA assays are provided (Table). For reliable results, it is essential that the recommended procedures be followed for collection and processing of blood to prepare plasma for HIV RNA measurements. Different plasma HIV RNA assays require

different plasma volumes (an important consideration in infants and in young children). These assays are best performed on plasma specimens prepared from blood obtained in collection tubes containing specific anticoagulants (e.g., ethylenediaminetetraacetic acid [EDTA] or acid-citrate-dextran [ACD]) (Table) (*44–46*).

Quantitative measurement of plasma HIV RNA levels can be expressed in two ways: a) the number of copies/mL of HIV RNA and b) the logarithm (to the base 10) of the number of copies/mL of HIV RNA. In clinically stable, HIV-infected adults, results obtained by using commercially available plasma HIV RNA assays can vary by approximately threefold (0.5 $\log_{10}$) in either direction on repeated measurements obtained within the same day or on different days (*35,36*). Factors influencing the variation seen in plasma HIV RNA assays include biological fluctuations and those introduced by the performance characteristics of the particular assay (*35,36,44–46*). Variability of current plasma HIV RNA assays is greater toward their lower limits of detection and consequently changes greater than 0.5 $\log_{10}$ HIV RNA copies can be seen near the assay detection limits without changes in clinical status (*35*). Differences greater than 0.5 $\log_{10}$ copies on repeated measures of plasma HIV RNA likely reflect biologically and clinically relevant changes. Increased variance toward the limit of assay detection presents an important consideration as the recommended target of suppression of HIV replication by antiretroviral therapy is now defined as being HIV RNA levels below the detection limit of plasma HIV RNA assays. Immune system activation (by immunizations or intercurrent infections) can lead to increased numbers of activated CD4+ T cells, and thereby result in increased levels of HIV replication (reflected by significant elevations of plasma HIV RNA levels from their baseline values) that may persist for as long as the inciting stimulus remains (*32–34*). Therefore, measurements obtained surrounding these events may not reflect a patient's actual steady-state level of plasma HIV RNA. Unlike CD4+ T cell count determinations, plasma HIV RNA levels do not exhibit diurnal variation (*26,36*). Within the large dynamic range of plasma HIV RNA levels that can be measured (varying over several $\log_{10}$ copies), the observed level of assay variance is low (Table). Measurement of two samples at baseline in clinically stable patients has been recommended as a way of reducing the impact of the variability of plasma HIV RNA assays (*19*), and recent data support this approach (*22*).

The level of viremia, as measured by the amount of HIV RNA in the plasma, accurately reflects the extent of virus replication in an infected person (*1,2,20,37*). Although the lymphoid tissues (e.g., lymph nodes and other compartments of the reticuloendothelial system) provide the major sites of active virus production in HIV-infected persons, virus produced in these tissues is released into the peripheral circulation where it can be readily sampled (*3,4,48*). Thus, plasma HIV RNA concentrations reflect the level of active virus replication throughout the body, although it is not known whether specific compartments (e.g., the central nervous system [CNS]) represent sites of infection that are not in direct communication with the peripheral pool of virus.

The Magnitude of HIV Replication in Infected Persons Determines Their Rate of Disease Progression

Plasma HIV RNA can be detected in virtually all HIV-infected persons although its concentration can vary widely depending on the stage of the infection (Figure 1) and on incompletely understood aspects of the host–virus interactions. During primary infection in adults when there are numerous target cells susceptible to HIV infection without a countervailing host immune response, concentrations of plasma HIV RNA can exceed 10^7 copies/mL (*83*). HIV disseminates widely throughout the body during this period, and many newly infected persons display symptoms of an acute viral illness, including fever, fatigue, pharyngitis, rash, myalgias, and headache (*84–86*). Coincident with the emergence of antiviral immune responses, concentrations of plasma HIV RNA decline precipitously (by 2 to 3 $\log_{10}$ copies or more). After a period of fluctuation, often lasting 6 months or more, plasma HIV RNA levels usually stabilize around a so-called set-point (*5,6,10,27,31,86*). The determinants of this set-point are incompletely understood but probably include the number of susceptible CD4+ T cells and macrophages available for infection, the degree of immune activation, and the tropism and replicative vigor (fitness) of the prevailing HIV strain at various times following the initial infection, as well as the effectiveness of the host anti-HIV immune response. In contrast to adults, HIV-infected infants often have very high levels of plasma HIV RNA that decline slowly with time and do not reach set-point levels until more than a year after infection (*14–18*).

Different infected persons display different steady-state levels of HIV replication. When populations of HIV-infected adults are studied in a cross-sectional manner, an inverse correlation between plasma HIV RNA levels and CD4+ T cell counts is seen (*87,88*). However, at any given CD4+ T cell count, plasma HIV RNA concentrations show wide interindividual variation (*87,88*). In established HIV infection, persistent concentrations of plasma HIV RNA range from <200 copies/mL in extraordinary persons who have apparently nonprogressive HIV infection to $>10^6$ copies/mL in persons who are in the advanced stages of immunodeficiency or are at risk for very rapid disease progression. In most HIV-infected and untreated adults, set-point plasma HIV RNA levels range between 10^3 and 10^5 copies/mL. Persons who have higher steady-state set-point levels of plasma HIV RNA generally lose CD4+ T cells more quickly, progress to AIDS more rapidly, and die sooner than those with lower HIV RNA set-point levels *(5–7,10,27)* (Figures 2–4). Once established, set-point HIV RNA levels can remain fairly constant for months to years. However, studies of populations of HIV-infected persons suggest a gradual trend toward increasing HIV RNA concentrations with time after infection (*10*). Within individual HIV-infected persons, rates of increase of plasma HIV RNA levels can change gradually, abruptly, or hardly at all (*10*). Progressively increasing plasma HIV RNA concentrations can signal the development of advancing immunodeficiency, regardless of the initial set-point value (*10,75*).

Plasma HIV RNA levels provide more powerful predictors of risk of progression to AIDS and death than do CD4+ T cell levels; however, the combined measurement of the two values provides an even more accurate method to assess the prognosis of HIV-infected persons (*27*). The relationship between baseline HIV RNA levels measured in a large cohort of HIV-infected adults and their subsequent rate of CD4+ T cell decline is shown (Figure 3) (*27*). Progressive loss of CD4+ T cells is observed in all

strata of baseline plasma HIV RNA concentrations, but substantially more rapid rates of decline are seen in persons who have higher baseline levels of plasma HIV RNA (Figure 3) (*27*) . Likewise, a clear gradient in risk for disease progression and death is seen with increasing baseline plasma HIV RNA levels (5,6,10,27) (Figures 2 and 4).

HIV Replicates Actively at All Stages of the Infection

The steady-state level of HIV RNA in the plasma is a function of the rates of production and clearance (i.e., the turnover) of the virus in circulation (1,2,20,21,37). Effective antiretroviral therapy perturbs this steady state and allows an assessment of the kinetic events that underlie it. Thus, virus clearance, the magnitude of virus production, and the longevity of virus-producing cells can all be measured. Recent studies in which measurements of virus and infected-cell turnover were analyzed in this way in persons who had moderate to advanced HIV disease have demonstrated that a very dynamic process of virus production and clearance underlies the seemingly static steady-state level of HIV virions in the plasma (*1,2,20,21,37*).

Within 2 weeks of initiation of potent antiretroviral therapy, plasma HIV RNA levels usually fall to approximately 1% of their initial values (*20,37*) (Figure 5). The slope of this initial decline reflects the clearance of virus from the circulation and the longevity of recently infected CD4+ T cells and is remarkably constant among different persons (*1,2,20,37*). The half-life of virions in circulation is exceedingly short—less than 6 hours. Thus, on average, half of the population of plasma virions turns over every 6 hours or less. Given such a rapid rate of virus clearance, it is estimated that 10^9 to 10^{10} (or more) virions must be produced each day to maintain the steady-state plasma HIV RNA levels typically found in persons who have moderate to advanced HIV disease (*20*). When new rounds of virus replication are blocked by potent antiretroviral drugs, virus production from the majority of infected cells (approximately 99%) continues for only a short period, averaging approximately 2 days (*1,2,20,37*). HIV-infected CD4+ T cells are lost, presumably as the result of direct cytopathic effects of virus infection, with an average half-life of an infected cell being approximately 1.25 days (*20*). The estimated generation time of HIV (the time from release of a virion until it infects another cell and results in the release of a new generation of virions) is approximately 2.5 days, which implies that the virus is replicating at a rate of approximately 140 or more cycles per year in an infected person (*20,21*). Thus, at the median period between initial infection and the diagnosis of AIDS, each virus genome present in an HIV-infected person is removed by more than a thousand generations from the virus that initiated the infection.

After the initial rapid decline in plasma HIV RNA levels following initiation of potent antiretroviral therapy, a slower decay of the remaining 1% of initial plasma HIV RNA levels is observed (*37*) (Figure 5). The length of this second phase of virus decay differs among different persons, lasting approximately 8–28 days. Most of the residual viremia is thought to arise from infected macrophages that are lost over an average half-life of about 2 weeks, whereas the remainder is produced following activation of latently infected CD4+ T cells that decay with an average half-life of about 8 days. Within 8 weeks of initiation of potent antiretroviral therapy (in previously untreated patients), plasma HIV RNA levels commonly fall below the level of detection of even the most sensitive plasma HIV RNA assays available (sensitivity of 25 copies HIV

RNA/mL), indicating that new rounds of HIV infection are profoundly suppressed (Figure 5) (*37*). Fortunately, this level of suppression of HIV replication appears to have been maintained for more than 16 months in most patients who adhere to effective combination antiretroviral drug regimens (*39*). However, even this marked pharmacologic interference of HIV replication has not yet been reported to eradicate an established infection. Those rare persons who have been studied after having stopped effective combination antiretroviral therapy following months with undetectable levels of plasma HIV RNA have all shown rapid rebounds in HIV replication. Furthermore, infectious HIV can still be isolated from CD4+ T cells obtained from antiretroviral treated persons whose plasma HIV RNA levels have been suppressed to undetectable levels (<50 copies/mL) for 2 years or more (*49,50*). Viruses recovered from these persons were demonstrated to be sensitive to the antiretroviral drugs used, indicating that a reservoir of latently infected resting CD4+ T cells exists that can maintain HIV infection for prolonged periods even when new cycles of virus replication are blocked. It is not known whether additional reservoirs of residual HIV infection exist in infected persons that can permit persistence of HIV infection despite profound inhibition of virus replication by effective combination antiretroviral therapies (*37,47,48*). HIV infection within the CNS represents an additional potential sanctuary for virus persistence, as many of the antiretroviral drugs now available do not efficiently cross the blood-brain barrier.

Active HIV Replication Continuously Generates Viral Variants That are Resistant to Antiretroviral Drugs

HIV replication depends on a virally encoded enzyme, RT (an RNA-dependent DNA polymerase) that copies the single-stranded viral RNA genome into a double-stranded DNA in an essential step in the virus life cycle (*21*). Unlike cellular DNA polymerases used to copy host cell chromosomal DNA during the course of cell replication, RT lacks a 3′ exonuclease activity that serves a "proofreading" function to repair errors made during transcription of the HIV genome. As a result, the HIV RT is an "error-prone" enzyme, making frequent errors while copying the RNA into DNA and giving rise to numerous mutations in the progeny virus genomes produced from infected cells. Estimates of the mutation rate of HIV RT predict that an average of one mutation is introduced in every one to three HIV genomes copied (*21,89*). Additional variation is introduced into the replicating population of HIV variants as a result of genetic recombination that occurs during the process of reverse transcription via template-switching between the two HIV RNA molecules that are included in each virus particle (*21,90*). Many mutations introduced into the HIV genome during the process of reverse transcription will compromise or abolish the infectivity of the virus; however, other mutations are compatible with virus infectivity. In HIV-infected persons, the actual frequency with which different genetic variants of HIV are seen is a function of their replicative vigor (fitness) and the nature of the selective pressures that may be acting on the existing swarm of genetic variants present (*21*). Important selective pressures that may exist in HIV-infected persons include their anti-HIV immune responses, the availability of host cells that are susceptible to virus infection in different tissues, and the use of antiretroviral drug treatments.

The rate of appearance of genetic variants of HIV within infected persons is a function of the number of cycles of virus replication that occurs during a person's infection (*20,21*). That numerous rounds of HIV replication are occurring daily in infected persons provides the opportunity to generate large numbers of variant viruses, including those that display diminished sensitivity to antiretroviral drugs. A mutation is probably introduced into every position of the HIV genome many times each day within an infected person, and the resulting HIV variants may accumulate within the resident virus population with successive cycles of virus replication (*21*). As a result of the great genetic diversity of the resident population of HIV, viruses harboring mutations that confer resistance to a given antiretroviral drug, and perhaps multiple antiretroviral drugs, are likely to be present in HIV-infected persons *before* antiretroviral therapy is initiated (*21*). Indeed, mutations that confer resistance to nucleoside analog RT inhibitors, NNRTIs, and PIs have been identified in HIV-infected persons who have never been treated with antiretroviral drugs (*61,91,92*). Once drug therapy is initiated, the pre-existing population of drug-resistant viruses can rapidly predominate. For drugs such as 3TC and nevirapine (and other NNRTIs), a single nucleotide change in the HIV RT gene can confer 100- to 1,000-fold reductions in drug susceptibility (*1,61,93–95*). Although these agents may be potent inhibitors of HIV replication, the antiretroviral activity of these drugs when used alone is largely reversed within 4 weeks of initiation of therapy due to the rapid outgrowth of drug-resistant variants (*1,61,93–95*). The rapidity with which drug-resistant variants emerge in this setting is consistent with the existence of drug-resistant subpopulations of HIV within infected patients before to the initiation of treatment (*21,61*). Because treatment with many of the available antiretroviral drugs selects for HIV variants that harbor the same or related mutations, specific treatments can select for the outgrowth of HIV variants that are resistant to drugs with which the patient has not been treated (referred to as cross-resistance) (*96,97*).

Drug-resistant viruses that emerge during drug therapy are predicted to replicate less well (are less fit) than their wild-type counterparts and are expected to attain lower steady-state levels of viral load than are present before the initiation of therapy (*21*). Evidence for such decreased fitness of drug-resistant viruses has been gleaned from studies of protease-inhibitor–treated or 3TC-treated patients, but this effect has not been apparent in NNRTI-treated patients (e.g., nevirapine or delavirdine) (*1,61*). Depending on its relative fitness, the drug-resistant variant can persist at appreciable levels even after the antiretroviral therapy that selected for its outgrowth is withdrawn. HIV variants resistant to nevirapine can persist for more than a year after withdrawal of nevirapine treatment (*61*). Zidovudine-resistant HIV variants and variants resistant to both zidovudine and nevirapine have also been shown to persist in infected persons and to replicate well enough to be transmitted from one person to another (*98*). Because HIV variants that are resistant to PIs often appear to be less fit than drug-sensitive viruses, their prevalence in patients who develop PI resistance may decline after withdrawal of the drug. However, although such variants may decline after drug withdrawal, they also may persist in patients at higher levels than their original levels and can be rapidly selected for should the same antiretroviral agent (or a PI demonstrating cross-resistance) be used again (*97*).

The definition of mutations associated with resistance to specific antiretroviral drugs and the advent of genetic methods to detect drug-resistant variants in treated

patients have raised the possibility of screening HIV-infected patients for the presence of HIV variants as a tool to guide therapeutic decisions (*92,99*). However, this approach must be considered experimental and may prove very difficult to implement because of the complex patterns of mutations that increase resistance to some antiretroviral agents. Furthermore, the prevalence of clinically important populations of drug-resistant variants in many HIV-infected persons is likely to be below the level of detection of the available assays, thus potentially creating falsely optimistic predictions of drug efficacy (*21,61*).

Combination Antiretroviral Therapy That Suppresses HIV Replication to Undetectable Levels Can Delay or Prevent the Emergence of Drug-Resistant Viral Variants

Current strategies for antiretroviral therapy are much more effective than those previously available, and the efficacy of these approaches confirms predictions emerging from fundamental studies of the biology of HIV infection. Several important principles have emerged from these studies that can be used to guide the application of antiretroviral therapies in clinical practice:

- The likelihood that HIV variants that are resistant to individual drugs (and possibly combinations of drugs) are already present in untreated patients must be appreciated.
- The likelihood that drug-resistant variants are already present in an HIV-infected person decreases as the number of noncross-resistant antiretroviral drugs used in combination is increased.
- The prevalence in untreated patients of HIV variants already resistant to antiretroviral agents that require multiple mutations in the virus target gene to confer high-level drug resistance is also expected to be lower as the number of required mutations increases. For example, high-level resistance to PIs (e.g., ritonavir and indinavir) requires the presence of multiple mutations in the HIV protease gene; some of these mutations affect the actual antiviral action of the drug, whereas others represent compensatory mutations that act to increase the fitness of the drug-resistant HIV variants (*96,97,100*). The prevalence of HIV variants that already harbor all of the mutations required for high-level resistance to these drugs is expected to be low in untreated patients.
- Antiretroviral drugs that select for partially disabled (less fit) viruses may benefit the host by decreasing the amount of virus replication (and consequent damage) that occurs even after drug-resistant mutants have overgrown drug-sensitive viruses.
- Incomplete suppression of HIV replication (as indicated by the continued presence of detectable levels of plasma HIV RNA) will afford the opportunity for continued accumulation of mutations that confer high-level drug resistance, and thereby facilitate the eventual outgrowth of the resistant virus population during continued therapy (*23,39*). The more effectively new cycles of HIV infection are suppressed, the fewer opportunities are provided for the accumulation of new

mutations that permit the emergence of drug-resistant variants (*97,100*). Thus, initiation and maintenance of therapy with optimal doses of combinations of potent antiretroviral drugs with the intent of suppressing HIV replication to levels below the detection limit of sensitive plasma HIV RNA assays provide the most promising strategy to forestall (or prevent) the emergence of drug-resistant viruses and achieve maximum protection from HIV-induced immune system damage.

Antiretroviral Therapy-Induced Inhibition of HIV Replication Predicts Clinical Benefit

As active HIV replication is directly linked to the progressive depletion of CD4+ T cell populations, reduction in levels of virus replication by antiretroviral drug therapy is predicted to correlate with the clinical benefits observed in treated patients. Data from an increasing number of clinical trials of antiretroviral agents provide strong support for this prediction and indicate that greater clinical benefit is obtained from more profound suppression of HIV replication (*9,13,23,38–40,56*). For example, virologic analyses from ACTG 175 (a study of zidovudine or didanosine monotherapy compared with combination therapy with zidovudine plus either didanosine or zalcitabine) indicate that a reduction in plasma HIV RNA levels to 1.0 log below baseline at 56 weeks after initiation of therapy was associated with a 90% reduction in risk of progression of clinical disease (*13*). In a pooled analysis of seven different ACTG studies, durable suppression of plasma HIV RNA levels to <5,000 copies of HIV RNA/mL between 1 and 2 years after initiation of treatment was associated with an average increase in CD4+ T cell levels of approximately 90 cells/mm^3 (*24*). Patients whose plasma HIV RNA levels failed to be stably suppressed to <5,000 copies/mL showed progressive decline in CD4+ T cell counts during the same period (*24*).

Decreases in plasma HIV RNA levels induced by antiretroviral therapy provide better indicators of clinical benefit than CD4+ T cell responses (*9,13,24*). Furthermore, in patients who have advanced HIV disease, clinical benefit correlates with treatment-induced decreases in plasma HIV RNA levels, even when CD4+ T cell increases are not seen. The failure to observe CD4+ T cell increases in some treated patients despite suppression of HIV replication may reflect irreversible damage to the regenerative capacity of the immune system in the later stages of HIV disease.

The most extensive data on the relationship between the magnitude of suppression of HIV replication induced by antiretroviral therapy and the degree of improved clinical outcome were generated during studies of nucleoside analog RT inhibitors used alone or in combination (*9,13,24*). These treatments yield less profound and less durable suppression of HIV replication than currently available combination therapy regimens that include potent PIs (and that are able to suppress HIV replication to levels below the detection limits of plasma HIV RNA assays) (*23,37,39*). Thus, it is likely that the relationship between suppression of HIV replication and clinical benefit will become even more apparent as experience with potent combination therapies accumulates.

Repair of immune system function may be incomplete following effective inhibition of continuing HIV replication and damage by antiretroviral drug therapy.

As discussed in the preceding principles, disease progression in HIV-infected patients results from active virus replication that inflicts chronic damage upon the function of the immune system and its structural elements, the lymphoid tissues. Because of the clonal nature of the antigen-specific immune response, in the absence of generation of immunocompetent CD4+ T cells from immature progenitor cells, it is likely that T cell responses may not be regained once lost, even if new rounds of HIV infection can be stopped by effective antiretroviral therapy (*80,82,101*). Similarly, it is not known if the damaged architecture of the lymphoid organs seen in persons with moderate to advanced HIV disease can be repaired following antiretroviral drug therapy. Should the residual proliferative potential of CD4+ and CD8+ T cells decline with increased duration of HIV infection and the magnitude of the cumulative loss and regeneration of lymphocyte populations, late introduction of antiretroviral therapy may have limited ability to reconstitute levels of functional lymphocytes. Thus, it is believed that the initiation of antiretroviral therapy before extensive immune system damage has occurred will be more effective in preserving and improving the ability of the HIV-infected person to mount protective immune responses.

Few reliable methods are now available to assess the integrity of immune responses in humans. However, the application of specific methods to the study of immune responses in HIV-infected patients before and after initiation of antiretroviral therapy indicates that immunologic recovery is incomplete even when HIV replication falls to undetectable levels. CD4+ T cell levels do not return to the normal range in most antiretroviral drug-treated patients, and the extent of CD4+ T cell increase is typically more limited when therapy is started in the later stages of HIV disease (*82*). Recent evidence indicates that the repertoire of antigen-specific CD4+ T cells becomes progressively constricted with declining T cell numbers (*82*). In persons who have evidence of a restricted T cell repertoire, antiretroviral therapy can increase total CD4+ T cell numbers but fails to increase the diversity of antigen recognition ability (*82*). It is not yet known if expansion of a constricted CD4+ T cell repertoire of antigen recognition might be seen with longer-term follow-up of such persons.

Reports of OIs occurring in antiretroviral-treated patients at substantially higher CD4+ T cell counts than those typically associated with susceptibility to the specific opportunistic infections raise the concern that restoration of protective immune responses may be incomplete, even when effective suppression of continuing HIV replication is achieved (*102*). However, other reports describe instances in which the clinical symptoms or signs of preexisting OIs were ameliorated (*103–105*), or in which new inflammatory responses to preexisting, but subclinical, OIs became manifest following initiation of effective combination antiretroviral therapy (*106,107*). These observations indicate that some improvement in immune function may be possible, even in patients who have advanced HIV disease, if sufficient numbers of pathogen-specific CD4+ T cells are still present when effective antiretroviral therapy is begun. The extent to which antiretroviral therapy can restore immune function when initiated in persons at varying stages of HIV disease is currently unknown but represents an essential question for future research.

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Appendices

TABLE. Characteristics of plasma HIV RNA assays*

Assay	Linear dynamic range† (copies/mL)	Observed intra-assay (copies/mL) standard deviation range (log_{10})§	Preferred anticoagulant
RT-PCR¶	4×10^2–$10^{5.2}$	<0.15–0.33	ACD/EDTA**
bDNA††	5×10^2–1.6×10^6	0.08–0.2	EDTA**
NASBA®§§	4×10^2–4×10^7	0.13–0.23	ACD/EDTA/HEP**

*More sensitive versions of each of these assays (detection limits 20–100 HIV RNA copies/mL) are currently in development and will likely be commercially available in the future.

†Higher values can be measured with dilution of the specimen into the linear dynamic range for each assay.

§Ranges are representative of those obtained in comparative analyses of plasma HIV RNA assays (*44–46*). Plasma HIV RNA assays tend to be more variable at or near the limit of quantitation. Thus, the significance of changes in HIV RNA levels at the lowest levels of quantitation for a given assay should be evaluated in light of this increased variability.

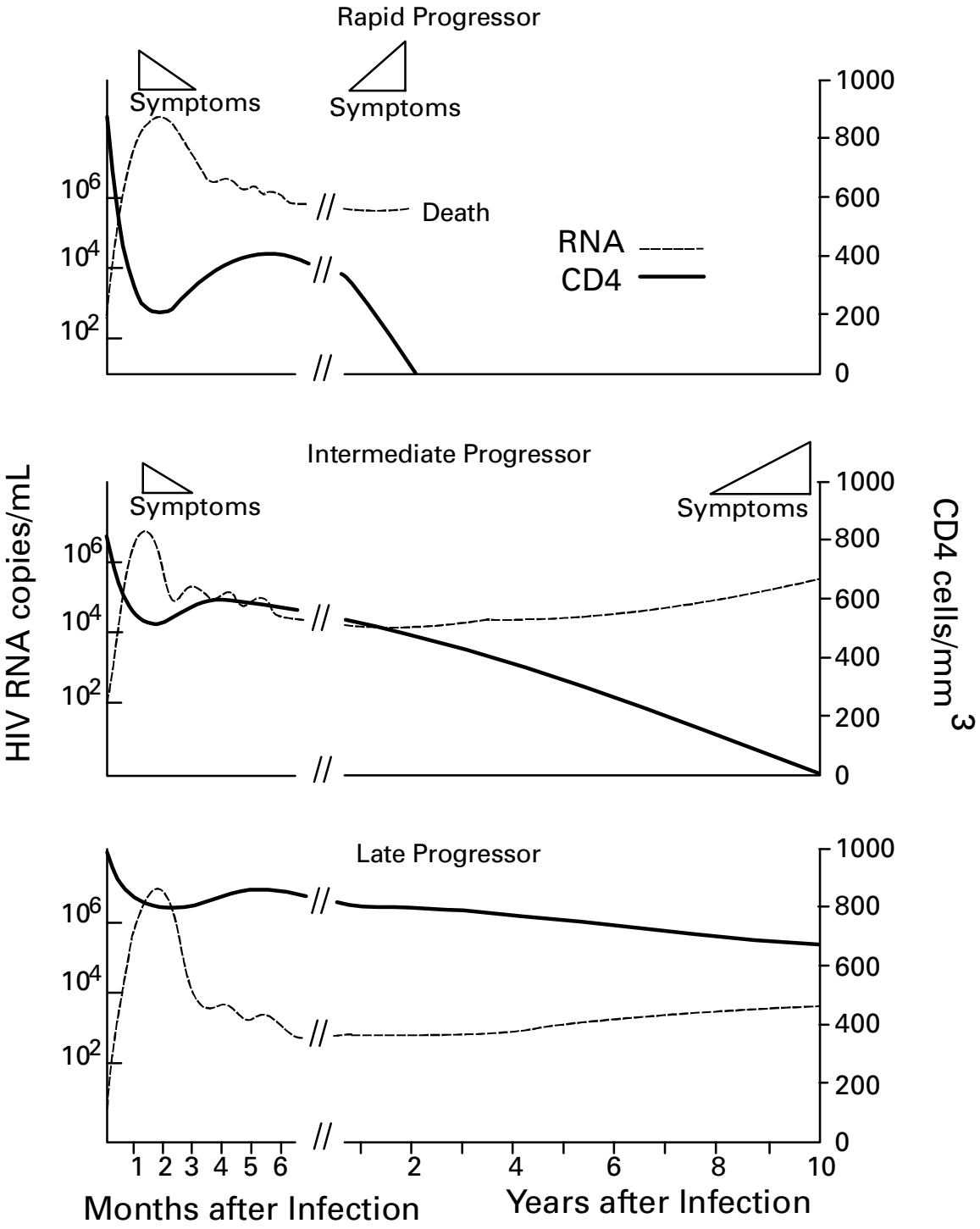
¶Amplicor HIV Monitor™ assay (Roche Molecular Systems, Alameda, CA).

**ACD = acid citrate dextran (citrate; yellow-top tube); EDTA = ethylenediaminetetraacetic acid (purple-top tube); HEP = heparin (green-top tube).

††Quantiplex™ HIV RNA bDNA assay (Chiron Diagnostics, Emeryville, CA).

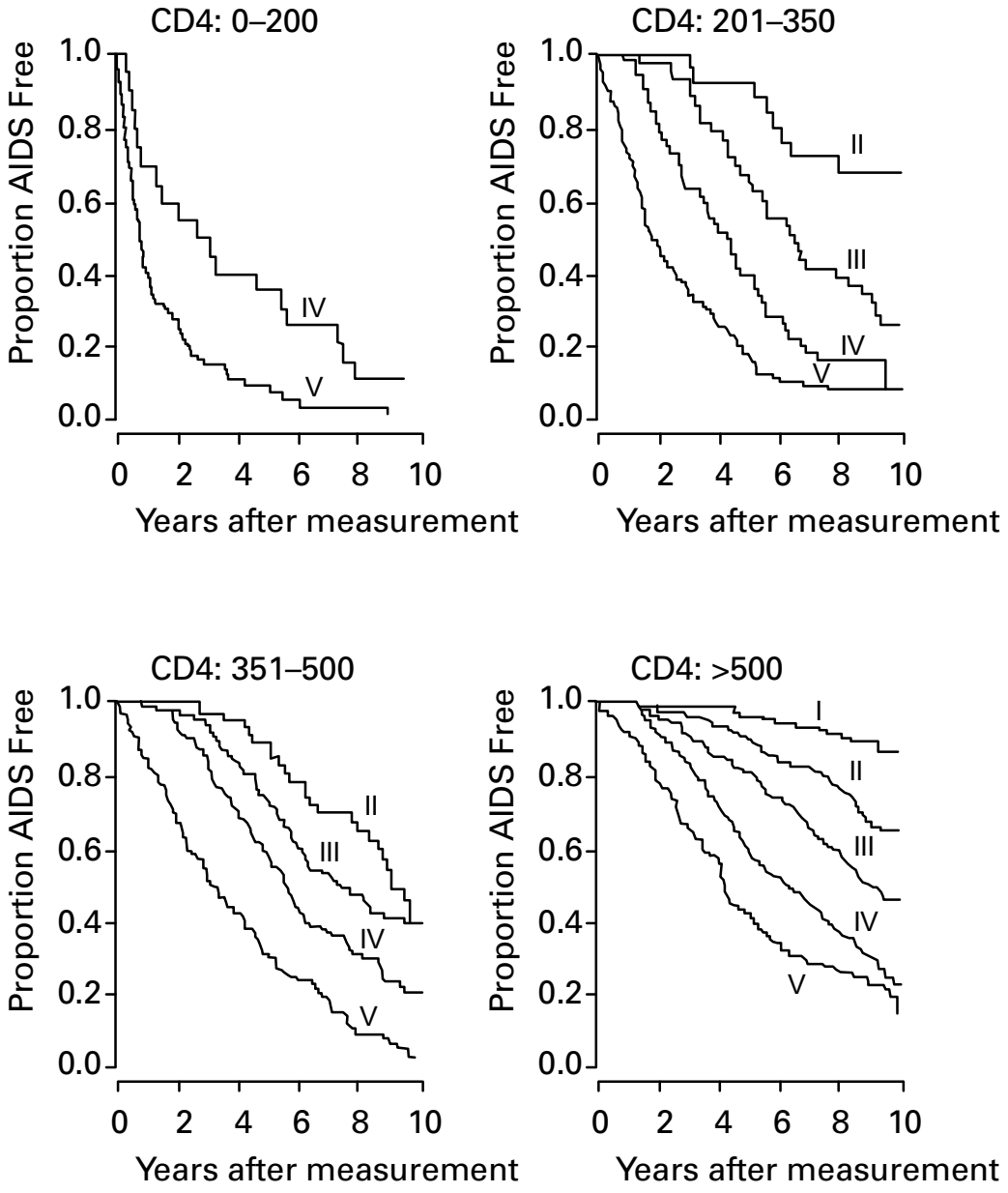
§§NucliSens™ HIV-1 QT assay (Organon Teknika, Boxtel, The Netherlands).

FIGURE 1. Generalized time course of HIV infection and disease



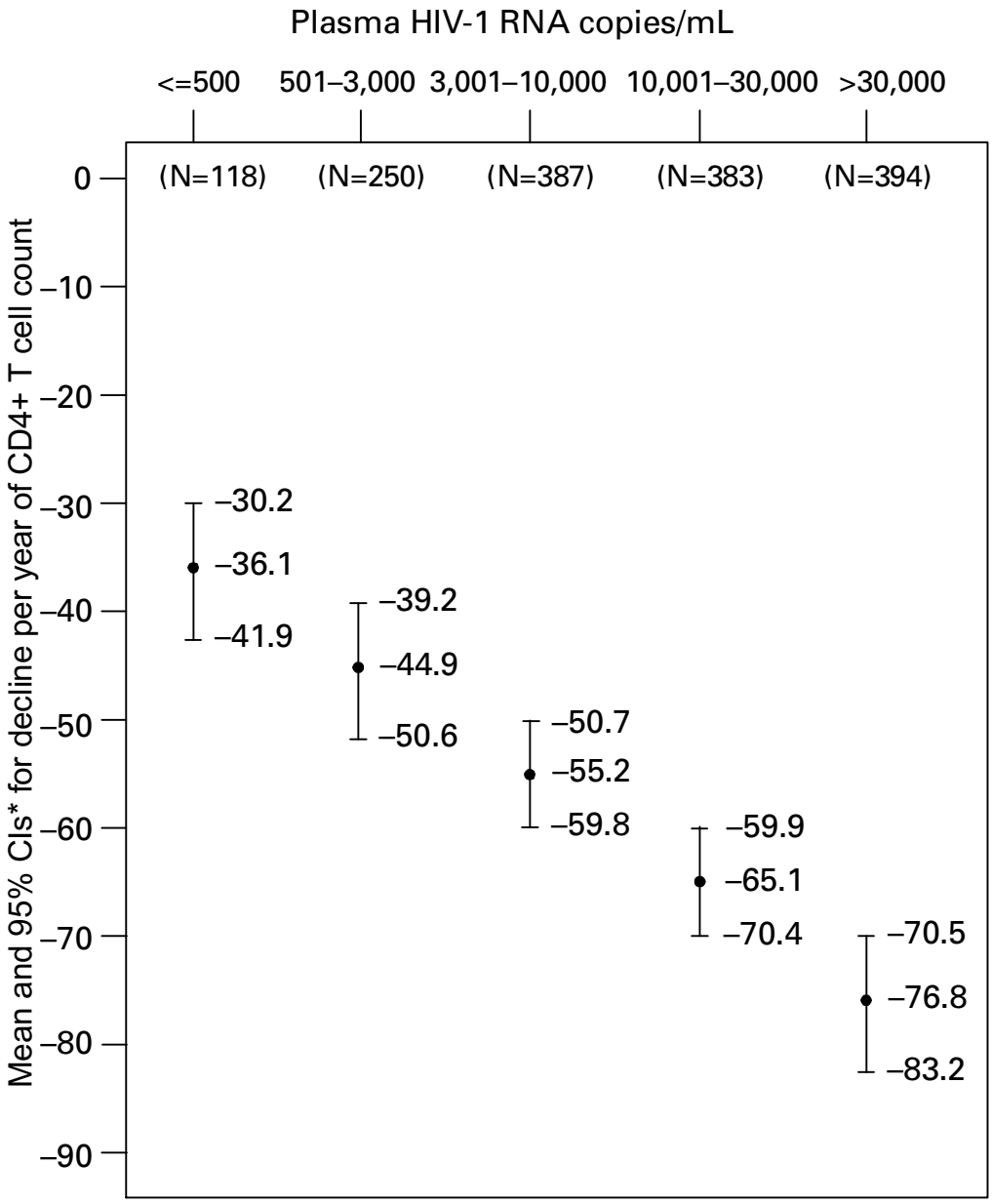
Three different patterns of disease progression: rapid, intermediate, and late progression.

FIGURE 2. AIDS-free survival by baseline plasma HIV RNA and CD4+ T cell levels



Kaplan-Meier curves showing AIDS-free survival by plasma HIV RNA category among groups of persons with different baseline CD4+ T cell counts who participated in the Multicenter AIDS Cohort Study (MACS) (27). The five categories of baseline HIV RNA levels were (I) ≤500; (II) 501–3,000; (III) 3,001–10,000; (IV) 10,001–30,000; and (V) >30,000 copies/mL. Within each CD4+ T cell category, baseline HIV RNA concentration provided significant discrimination of AIDS-free times ($p<0.001$) and survival times (27). In the lowest CD4+ T cell category (<200 cells/mm^3), there were too few participants with HIV RNA concentrations of ≤10,000 copies/mL to provide reliable estimates for RNA categories I-III. In the next lowest CD4+ T cell categories (201–350 and 351–500 cells/mm^3), there were too few participants with HIV RNA concentrations of ≤500 copies/mL (category I) to provide reliable estimates. Plasma HIV RNA concentrations were measured using the Quantiplex™ HIV RNA bDNA assay.

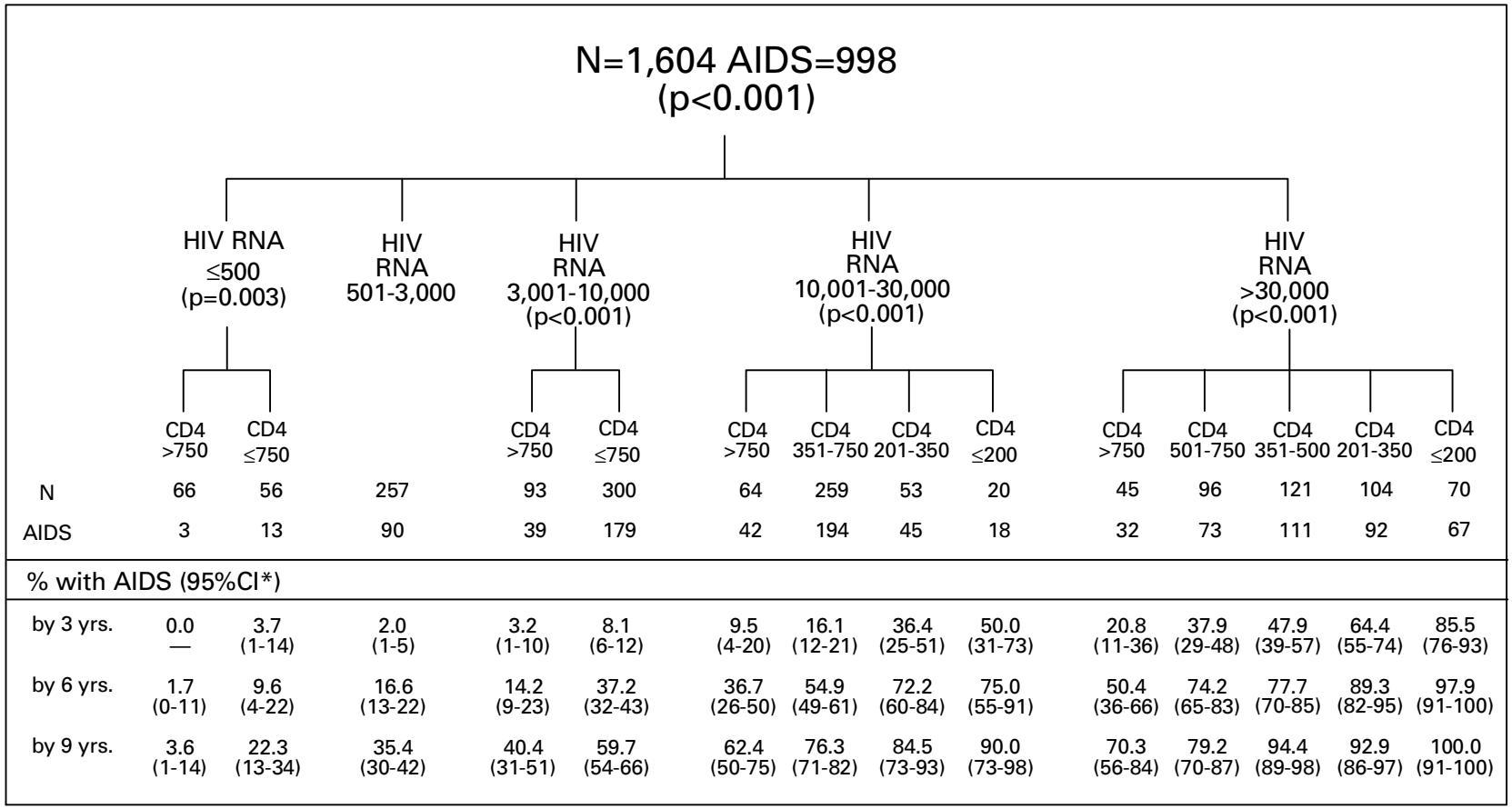
FIGURE 3. Association between rates of decline of CD4+ T cell counts and baseline plasma HIV RNA level



*Confidence intervals.

The relationship between baseline HIV-1 RNA level and the subsequent rate of decline in CD4+ T cells seen in participants of the Multicenter AIDS Cohort Study (MACS) (*27*). The study population was divided into five categories of plasma HIV-1 RNA defined by baseline concentrations of (I) ≤500; (II) 501–3,000; (III) 3,001–10,000; (IV) 10,001–30,000; and (V) >30,000 copies/mL. The estimated mean slope of decline in CD4+ T cells (number of cells lost per year) and 95% CIs by plasma HIV-1 RNA category are shown. The estimated rates of decline in CD4+ T cell counts are substantially different for each of the five baseline HIV RNA categories and show a monotonic relationship; i.e., the higher the baseline HIV RNA concentration, the greater the rate of decline of CD4+ T cell count. Plasma HIV RNA concentrations were measured using the Quantiplex™ HIV RNA bDNA assay.

FIGURE 4. Probability of AIDS by baseline HIV RNA level and CD4+ T cell count

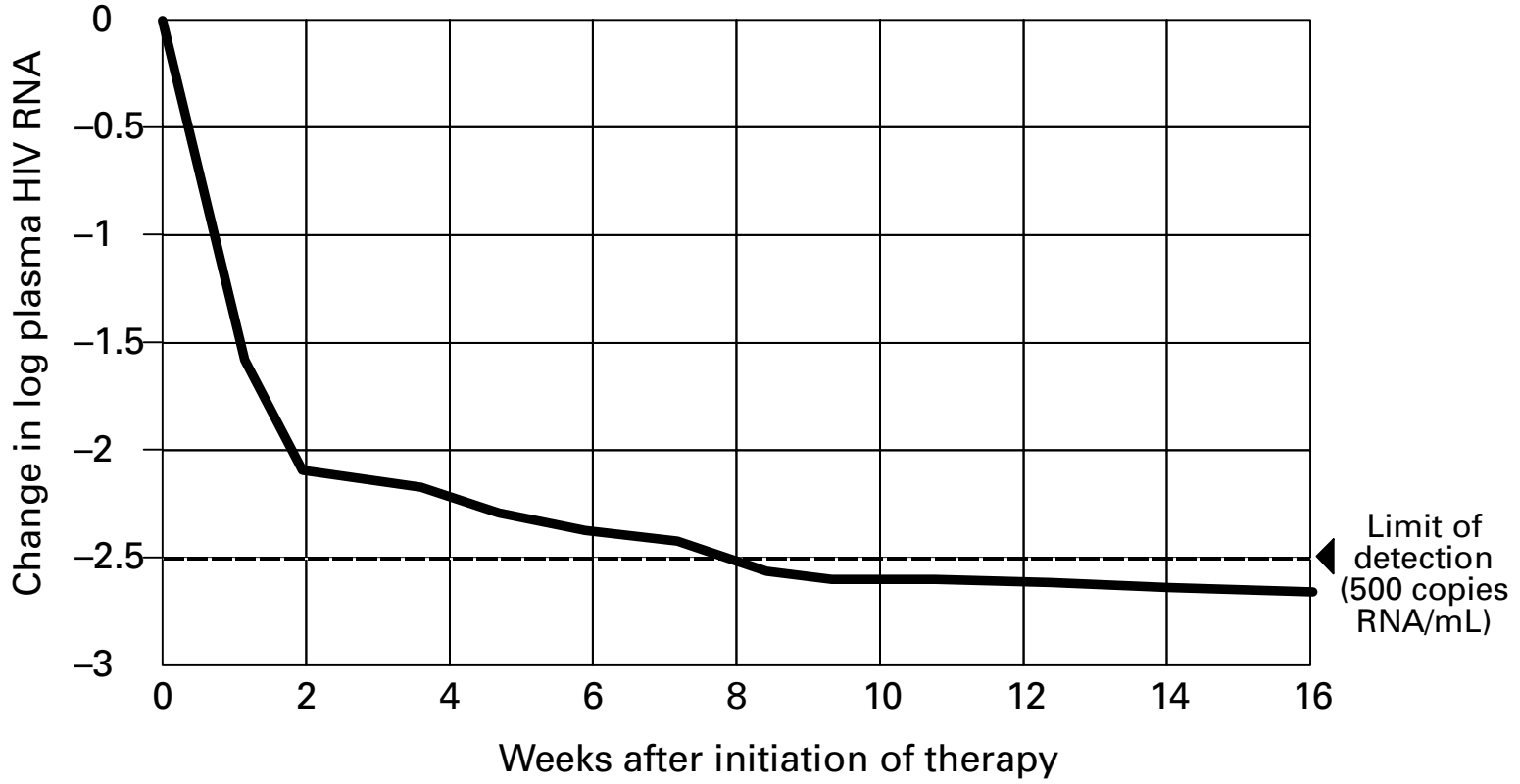


	HIV RNA ≤500 (p=0.003)		HIV RNA 501-3,000	HIV RNA 3,001-10,000 (p<0.001)		HIV RNA 10,001-30,000 (p<0.001)				HIV RNA >30,000 (p<0.001)				
	CD4 >750	CD4 ≤750		CD4 >750	CD4 ≤750	CD4 >750	CD4 351-750	CD4 201-350	CD4 ≤200	CD4 >750	CD4 501-750	CD4 351-500	CD4 201-350	CD4 ≤200
N	66	56	257	93	300	64	259	53	20	45	96	121	104	70
AIDS	3	13	90	39	179	42	194	45	18	32	73	111	92	67
% with AIDS (95%CI*)														
by 3 yrs.	0.0 —	3.7 (1-14)	2.0 (1-5)	3.2 (1-10)	8.1 (6-12)	9.5 (4-20)	16.1 (12-21)	36.4 (25-51)	50.0 (31-73)	20.8 (11-36)	37.9 (29-48)	47.9 (39-57)	64.4 (55-74)	85.5 (76-93)
by 6 yrs.	1.7 (0-11)	9.6 (4-22)	16.6 (13-22)	14.2 (9-23)	37.2 (32-43)	36.7 (26-50)	54.9 (49-61)	72.2 (60-84)	75.0 (55-91)	50.4 (36-66)	74.2 (65-83)	77.7 (70-85)	89.3 (82-95)	97.9 (91-100)
by 9 yrs.	3.6 (1-14)	22.3 (13-34)	35.4 (30-42)	40.4 (31-51)	59.7 (54-66)	62.4 (50-75)	76.3 (71-82)	84.5 (73-93)	90.0 (73-98)	70.3 (56-84)	79.2 (70-87)	94.4 (89-98)	92.9 (86-97)	100.0 (91-100)

*Confidence interval.

A regression tree containing 14 distinct categories of risk of progression to AIDS defined among participants in the Multicenter AIDS Cohort Study (MACS) (27). The risk of progression to AIDS can be assessed for many infected persons through the combined analysis of their baseline HIV RNA levels and CD4+ T cell counts. The number of study participants in each group is indicated by "N." AIDS risk with 95% CIs appear at the bottom of the figure. Plasma HIV RNA concentrations were measured using the Quantiplex™ HIV RNA bDNA assay.

FIGURE 5. Rate of decline of plasma HIV RNA concentration after initiation of potent combination antiretroviral therapy



A representative time course of rate of decline in plasma HIV RNA concentration (in $\log_{10}$ copies of RNA/mL) following initiation of a potent regimen of combination antiretroviral therapy (e.g., two nucleoside analog reverse transcriptase inhibitors [such as zidovudine and lamivudine] plus a potent, bioavailable protease inhibitor [such as indinavir, nelfinavir, or ritonavir]). The first phase of decline is a rapid, approximately 2 $\log_{10}$ (100-fold) fall in plasma HIV RNA concentrations. The slope of this first phase of decline in plasma RNA levels is very similar between different persons initiating effective antiretroviral therapies. A second, more gradual phase of decline in plasma HIV RNA levels is seen over subsequent weeks, the slope of which varies between different treated persons. Many effectively treated persons will demonstrate declines in plasma RNA levels to below the limits of assay detection (500 copies RNA/mL) by approximately 8 weeks after initiation of antiretroviral therapy, although some persons may take longer to demonstrate undetectable virus. (*37,39*). When plasma HIV RNA levels fall below detection, the absolute nadir is unknown. However, plasma HIV RNA levels have decreased below the detection limits of even more sensitive assays (sensitivity of 25 RNA copies/mL) in many effectively treated persons.

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Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*

Summary

With the development and FDA approval of an increasing number of antiretroviral agents, decisions regarding the treatment of HIV-infected persons have become complex; and the field continues to evolve rapidly. In 1996, the Department of Health and Human Services and the Henry J. Kaiser Family Foundation convened the Panel on Clinical Practices for the Treatment of HIV to develop guidelines for the clinical management of HIV-infected persons. This report includes the guidelines developed by the Panel regarding the use of laboratory testing in initiating and managing antiretroviral therapy, considerations for initiating therapy, whom to treat, what regimen of antiretroviral agents to use, when to change the antiretroviral regimen, treatment of the acutely HIV-infected person, special considerations in adolescents, and special considerations in pregnant women. Viral load and CD4+ T cell testing should ideally be performed twice before initiating or changing an antiretroviral treatment regimen. All patients who have advanced or symptomatic HIV disease should receive aggressive antiretroviral therapy. Initiation of therapy in the asymptomatic person is more complex and involves consideration of multiple virologic, immunologic, and psychosocial factors. In general, persons who have <500 CD4+ T cells per mm^3 should be offered therapy; however, the strength of the recommendation to treat should be based on the patient's willingness to accept therapy as well as the prognosis for AIDS-free survival as determined by the HIV RNA copy per mL of plasma and the CD4+ T cell count. Persons who have >500 CD4+ T cells per mm3 can be observed or can be offered therapy; again, risk of progression to AIDS, as determined by HIV RNA viremia and CD4+ T cell count, should guide the decision to treat. Once the decision to initiate antiretroviral therapy has been made, treatment should be aggressive with the goal of maximal viral suppression. In general, a protease inhibitor and two non-nucleoside reverse transcriptase inhibitors should be used initially. Other regimens may be utilized but are considered less than optimal. Many factors, including reappearance of previously undetectable HIV RNA, may indicate treatment failure. Decisions to change therapy and decisions regarding new regimens must be carefully considered; there are minimal clinical data to guide these decisions. Patients with acute HIV infection should probably be administered aggressive antiretroviral therapy; once initiated, duration of treatment is unknown and will likely need to continue for several years, if not for life. Special considerations apply to adolescents and pregnant women and are discussed in detail.

*Information included in these guidelines may not represent FDA approval or approved labeling for the particular products or indications in question. Specifically, the terms "safe" and "effective" may not be synonymous with the FDA-defined legal standards for product approval.

INTRODUCTION

These guidelines were developed by the Panel on Clinical Practices for Treatment of HIV Infection, convened by the Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation. The guidelines contain recommendations for the clinical use of antiretroviral agents in the treatment of adults and adolescents (defined in Considerations for Antiretroviral Therapy in the HIV-Infected Adolescent) who are infected with the human immunodeficiency virus (HIV). Guidance for the use of antiretroviral treatment in pediatric HIV infection is not contained in this report. Although the pathogenesis of HIV infection and the general virologic and immunologic principles underlying the use of antiretroviral therapy are similar for all HIV-infected persons, unique therapeutic and management considerations apply to HIV-infected children. In recognition of these differences, a separate set of guidelines will address pediatric-specific issues related to antiretroviral therapy.

These guidelines are intended for use by physicians and other health-care providers who use antiretroviral therapy to treat HIV-infected adults and adolescents. The recommendations contained herein are presented in the context of and with reference to the first section of this report, Principles of Therapy for HIV Infection, formulated by the National Institutes of Health (NIH) Panel to Define Principles of Therapy of HIV Infection. Together, these reports provide the pathogenesis-based rationale for therapeutic strategies as well as practical guidelines for implementing these strategies. Although the guidelines represent the current state of knowledge regarding the use of antiretroviral agents, this field of science is rapidly evolving, and the availability of new agents or new clinical data regarding the use of existing agents will result in changes in therapeutic options and preferences. The Antiretroviral Working Group, a subgroup of the Panel, will meet several times a year to review new data; recommendations for changes in this document would then be submitted to the Panel and incorporated as appropriate. Copies of this document and all updates are available from the CDC National AIDS Clearinghouse (1-800-458-5231) and are posted on the Clearinghouse World-Wide Web site (http://www.cdcnac.org). In addition, copies and updates also are available from the HIV/AIDS Treatment Information Service (1-800-448-0440; Fax 301-519-6616; TTY 1-800-243-7012) and on the ATIS World-Wide Web site (http://www.hivatis.org). Readers should consult these web sites regularly for updates in the guidelines. These recommendations are not intended to substitute for the judgment of a physician who is expert in caring for HIV-infected persons. When possible, the treatment of HIV-infected patients should be directed by a physician with extensive experience in the care of these patients. When this is not possible, the physician treating the patient should have access to such expertise through consultations.

Each recommendation is accompanied by a rating that includes a letter and a Roman numeral (Table 1), similar to the rating schemes described in previous guidelines on the prophylaxis of opportunistic infections (OIs) issued by the U.S. Public Health Service and the Infectious Diseases Society of America (*1*). The letter indicates the strength of the recommendation based on the opinion of the Panel, and the Roman numeral rating reflects the nature of the evidence for the recommendation (Table 1). Thus, recommendations based on data from clinical trials with clinical endpoints are differentiated from recommendations based on data derived from clinical trials with laboratory endpoints (e.g., CD4+ T cell count or plasma HIV RNA levels); when clinical

trial data are not available, recommendations are based on the opinions of experts familiar with the relevant scientific literature. The majority of current clinical trial data regarding the use of antiretroviral agents has been obtained in trials enrolling predominantly young to middle-aged males. Although current knowledge indicates that women may differ from men in the absorption, metabolism, and clinical effects of certain pharmacologic agents, clinical experience and data available to date do not indicate any substantial sex differences that would modify these guidelines. However, theoretical concerns exist, and the Panel urges continuation of the current efforts to enroll more women in antiretroviral clinical trials so that the data needed to re-evaluate this issue can be gathered expeditiously.

This report addresses the following issues: the use of testing for plasma HIV RNA levels (viral load) and CD4+ T cell count; initiating therapy in established HIV infection; initiating therapy in patients who have advanced-stage HIV disease; interruption of antiretroviral therapy; changing therapy and available therapeutic options; the treatment of acute HIV infection; antiretroviral therapy in adolescents; and antiretroviral therapy in the pregnant woman.

USE OF TESTING FOR PLASMA HIV RNA LEVELS AND CD4+ T CELL COUNT IN GUIDING DECISIONS FOR THERAPY

Decisions regarding either initiating or changing antiretroviral therapy should be guided by monitoring the laboratory parameters of both plasma HIV RNA (viral load) and CD4+ T cell count and by assessing the clinical condition of the patient. Results of these two laboratory tests provide the physician with important information about the virologic and immunologic status of the patient and the risk of disease progression to acquired immunodeficiency syndrome (AIDS) (see Principle 2 in the first section of this report). HIV viral load testing has been approved by the U.S. Food and Drug Administration (FDA) only for the RT-PCR assay (Roche) and only for determining disease prognosis. However, data presented at an FDA Advisory Committee for the Division of Antiviral Drug Products (July 14–15, 1997, Silver Spring, MD) provide further evidence for the utility of viral RNA testing in monitoring therapeutic responses. Multiple analyses of more than 5,000 patients who participated in approximately 18 trials with viral load monitoring demonstrated a reproducible dose-response type association between decreases in plasma viremia and improved clinical outcome based on standard endpoints of new AIDS-defining diagnoses and survival. This relationship was observed over a range of patient baseline characteristics, including pretreatment plasma RNA level, CD4+ T cell count, and prior drug experience. The consensus of the Panel is that viral load testing is the essential parameter in decisions to initiate or change antiretroviral therapies. Measurement of plasma HIV RNA levels (viral load), using quantitative methods, should be performed at the time of diagnosis of HIV infection and every 3–4 months thereafter in the untreated patient (AIII) (Table 2). CD4+ T cell counts should be measured at the time of diagnosis and generally every 3–6 months thereafter (AIII). These intervals between tests are merely recommendations, and flexibility should be exercised according to the circumstances of the individual case. Plasma HIV RNA levels also should be measured immediately prior to and again at 4–8 weeks after initiation of antiretroviral therapy (AIII). This second time point allows the clinician to evaluate the initial effectiveness of therapy because in most patients, ad-

herence to a regimen of potent antiretroviral agents should result in a large decrease (~0.5 to 0.75 $\log_{10}$) in viral load by 4–8 weeks. The viral load should continue to decline over the following weeks, and in most persons it becomes below detectable levels (currently defined as <500 RNA copies/mL) by 12–16 weeks of therapy. The speed of viral load decline and the movement toward undetectable are affected by the baseline CD4+ T cell count, the initial viral load, potency of the regimen, adherence, prior exposure to antiretroviral agents, and the presence of any OIs. These individual differences must be considered when monitoring the effect of therapy. However, the absence of a virologic response of the magnitude previously described (i.e., ~0.5 to 0.75 $\log_{10}$ by 4–8 weeks and undetectable by 12–16 weeks) should prompt the physician to reassess patient adherence, rule out malabsorption, consider repeat RNA testing to document lack of response, and/or consider a change in drug regimen. Once the patient is on therapy, HIV RNA testing should be repeated every 3–4 months to evaluate the continuing effectiveness of therapy (AII). With optimal therapy, viral levels in plasma at 6 months should be undetectable (i.e., <500 copies of HIV RNA per mL of plasma) (*2*). If HIV RNA remains above 500 copies/mL in plasma after 6 months of therapy, the plasma HIV RNA test should be repeated to confirm the result, and a change in therapy should be considered according to the guidelines provided in "Considerations for Changing a Failing Regimen" (BIII). More sensitive viral load assays are in development that can quantify HIV RNA down to approximately 50 copies/mL. Preliminary data from clinical trials strongly suggest that lowering plasma HIV RNA to below 50 copies/mL is associated with a more complete and durable viral suppression, compared with reducing HIV RNA to levels between 50–500 copies/mL. However, the clinical significance of these findings is currently unclear.

When deciding whether to initiate therapy, the CD4+ T cell count and plasma HIV RNA measurement ideally should be performed on two occasions to ensure accuracy and consistency of measurement (BIII). However, in patients with advanced HIV disease, antiretroviral therapy should generally be initiated after the first viral load measurement is obtained to prevent a potentially deleterious delay in treatment. Although the requirement for two measurements of viral load may place a substantial financial burden on patients or payers, two measurements of viral load should provide the clinician with the best information for subsequent follow-up of the patient. Plasma HIV RNA levels should not be measured during or within 4 weeks after successful treatment of any intercurrent infection, resolution of symptomatic illness, or immunization (see Principle 2). Because differences exist among commercially available tests, confirmatory plasma HIV RNA levels should be measured by the same laboratory using the same technique to ensure consistent results.

A substantial change in plasma viremia is considered to be a threefold or 0.5 $\log_{10}$ increase or decrease. A substantial decrease in CD4+ T cell count is a decrease of >30% from baseline for absolute cell numbers and a decrease of >3% from baseline in percentages of cells (*3,4*). Discordance between trends in CD4+ T cell numbers and plasma HIV RNA levels can occur and was found in 20% of patients in one cohort studied (*5*). Such discordance can complicate decisions regarding antiretroviral therapy and may be due to several factors that affect plasma HIV RNA testing (see Principle 2). Viral load and trends in viral load are considered to be more informative for guiding decisions regarding antiretroviral therapy than are CD4+ T cell counts; exceptions to this rule do occur, however (see Considerations for Changing a Failing

Regimen); when changes in viral loads and CD4+ T cell counts are discordant, expert consultation should be considered.

ESTABLISHED HIV INFECTION

Patients who have established HIV infection are considered in two arbitrarily defined clinical categories: 1) asymptomatic infection or 2) symptomatic disease (e.g., wasting, thrush, or unexplained fever for ≥2 weeks), including AIDS, defined according to the 1993 CDC classification system (6). All patients in the second category should be offered antiretroviral therapy. Considerations for initiating antiretroviral therapy in the first category of patients (i.e., patients who are asymptomatic) are complex and are discussed separately in the following section. However, before initiating therapy in any patient, the following evaluation should be performed:

- Complete history and physical (AII)
- Complete blood count, chemistry profile (AII)
- CD4+ T cell count (AI)
- Plasma HIV RNA measurement (AI)

Additional evaluation should include routine tests pertinent to the prevention of OIs, if not already performed (i.e., VDRL, tuberculin skin test, toxoplasma IgG serology, and gynecologic exam with Pap smear), and other tests as clinically indicated (e.g., chest radiograph, hepatitis C virus [HCV] serology, ophthalmologic exam) (AII). Hepatitis B virus (HBV) serology is indicated for a patient who is a candidate for the hepatitis B vaccine or who has abnormal liver function tests (AII); cytomegalovirus (CMV) serology may be useful in certain persons, as discussed in *1997 USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With the Human Immunodeficiency Virus* (*1*) (BIII).

Considerations for Initiating Therapy in the Patient Who Has Asymptomatic HIV Infection

It has been demonstrated that antiretroviral therapy provides clinical benefit in HIV-infected persons who have advanced HIV disease and immunosuppression (*7–11*). Although there is theoretical benefit to treating patients who have CD4+ T cells >500 cells/mm^3 (see Principle 3), no long-term clinical benefit of treatment has yet been demonstrated. A major dilemma confronting patients and practitioners is that the antiretroviral regimens currently available that have the greatest potency in terms of viral suppression and CD4+ T cell preservation are medically complex, are associated with several specific side effects and drug interactions, and pose a substantial challenge for adherence. Thus, decisions regarding treatment of asymptomatic, chronically infected persons must balance a number of competing factors that influence risk and benefit.

The physician and the asymptomatic patient must consider multiple risks and benefits in deciding when to initiate therapy (Table 3) (see Principle 3). Several factors influence the decision to initiate early therapy: the real or potential goal of maximally

suppressing viral replication; preserving immune function; prolonging health and life; decreasing the risk of drug resistance due to early suppression of viral replication with potent therapy; and decreasing drug toxicity by treating the healthier patient. Factors weighing against early treatment in the asymptomatic stable patient include the following: the potential adverse effects of the drugs on quality of life, including the inconvenience of most of the maximally suppressive regimens currently available (e.g., dietary change or large numbers of pills); the potential risk of developing drug resistance despite early initiation of therapy; the potential for limiting future treatment options due to cycling of the patient through the available drugs during early disease; the potential risk of transmission of virus resistant to protease inhibitors and other agents; the unknown durability of effect of the currently available therapies; and the unknown long-term toxicity of some drugs. Thus, the decision to begin therapy in the asymptomatic patient is complex and must be made in the setting of careful patient counseling and education. The factors that must be considered in this decision include the following: 1) the willingness of the individual to begin therapy; 2) the degree of existing immunodeficiency as determined by the CD4+ T cell count; 3) the risk for disease progression as determined by the level of plasma HIV RNA (Table 4; Figure); 4) the potential benefits and risks of initiating therapy in asymptomatic persons, as discussed above; and 5) the likelihood, after counseling and education, of adherence to the prescribed treatment regimen. In regard to adherence, no patient should automatically be excluded from consideration for antiretroviral therapy simplyecause he or she exhibits a behavior or other characteristic judged by some to lend itself to noncompliance. The likelihood of patient adherence to a complex drug regimen should be discussed and determined by the individual patient and physician before therapy is initiated. To achieve the level of adherence necessary for effective therapy, providers are encouraged to utilize strategies for assessing and assisting adherence that have been developed in the context of chronic treatment for other serious diseases. Intensive patient education regarding the critical need for adherence should be provided, specific goals of therapy should be established and mutually agreed upon, and a long-term treatment plan should be developed with the patient. Intensive follow-up should take place to assess adherence to treatment and to continue patient counseling to prevent transmission of HIV through sexual contact and injection of drugs.

Initiating Therapy in the Patient Who Has Asymptomatic HIV Infection

Once the patient and physician have decided to initiate antiretroviral therapy, treatment should be aggressive, with the goal of maximal suppression of plasma viral load to undetectable levels. Recommendations regarding when to initiate therapy and what regimens to use are provided (Tables 5 and 6). In general, any patient who has <500 CD4+ T cells/mm^3 or >10,000 (bDNA) or 20,000 (RT-PCR) copies of HIV RNA/mL of plasma should be offered therapy (AII). However, the strength of the recommendation for therapy should be based on the readiness of the patient for treatment and a consideration of the prognosis for risk for progression to AIDS as determined by viral load, CD4+ T cell count (Table 4; Figure), and the slope of the CD4+ T cell count decline. The values for bDNA (Table 4; Figure, first column or line) are the uncorrected HIV RNA values obtained from the Multicenter AIDS Cohort Study (MACS). It had previously

been thought that these values, obtained on stored heparinized plasma specimens, should be multiplied by a factor of two to adjust for an anticipated twofold loss of RNA ascribed to the effects of heparin and delayed processing on the stability of RNA. However, more recent analysis suggests that the reduction ascribed to these factors is ≤0.2 log, so that no significant correction factor is necessary (Mellors J, personal communication, October 1997). RT-PCR values also are provided (Table 4; Figure); comparison of the results obtained from the RT-PCR and bDNA assays, using the manufacturer's controls, consistently indicates that the HIV-1 RNA values obtained by RT-PCR are approximately twice those obtained by the bDNA assay (12). Thus, the MACS values must be multiplied by approximately 2 to be consistent with current RT-PCR values. A third test for HIV RNA, the nucleic acid sequence based amplification (NASBA®), is currently used in some clinical settings. However, formulas for converting values obtained from either branched DNA (bDNA) or RT-PCR assays to NASBA®-equivalent values cannot be derived from the limited data currently available.

Currently, there are two general approaches to initiating therapy in the asymptomatic patient: a) a therapeutically more aggressive approach in which most patients would be treated early in the course of HIV infection due to the recognition that HIV disease is virtually always progressive and b) a therapeutically more cautious approach in which therapy may be delayed because the balance of the risk for clinically significant progression and other factors discussed above are considered to weigh in favor of observation and delayed therapy. The aggressive approach is heavily based on the Principles of Therapy, particularly the principle (see Principle 3) that one should begin treatment before the development of significant immunosuppression and one should treat to achieve undetectable viremia; thus, all patients who have <500 CD4+ T cells/mm^3 would be started on therapy as would patients who have higher CD4+ T cell numbers and plasma viral load >10,000 (bDNA) or 20,000 (RT-PCR) (Table 5). The more conservative approach to the initiation of therapy in the asymptomatic person would delay treatment of the patient who has <500 CD4+ T cells/mm^3 and low levels of viremia and who has a low risk for rapid disease progression (Table 4); careful observation and monitoring would continue. Patients who have CD4+ T cell counts >500/mm^3 would also be observed, except those who are at substantial risk for rapid disease progression because of a high viral load. For example, the patient who has 60,000 (RT-PCR) or 30,000 (bDNA) copies of HIV RNA/mL, regardless of CD4+ T cell count, has a high probability of progressing to an AIDS-defining complication of HIV disease within 3 years (32.6% if CD4+ T cells are >500/mm^3) and should clearly be encouraged to initiate antiretroviral therapy. Conversely, a patient who has 18,000 copies of HIV RNA/mL of plasma, measured by RT-PCR, and a CD4+ T cell count of 410/mm^3, has a 5.9% chance of progressing to an AIDS-defining complication of HIV infection in 3 years (Table 4). The therapeutically aggressive physician would recommend treatment for this patient to suppress the ongoing viral replication that is readily detectable; the therapeutically more conservative physician would discuss the possibility of initiation of therapy but recognize that a delay in therapy because of the balance of considerations previously discussed also is reasonable. In either case, the patient should make the final decision regarding acceptance of therapy following discussion with the health-care provider regarding specific issues relevant to his/her own clinical situation.

When initiating therapy in the patient who has never been administered antiretroviral therapy, one should begin with a regimen that is expected to reduce viral replication to undetectable levels (AIII). Based on the weight of experience, the preferred regimen to accomplish this consists of two nucleoside reverse transcriptase inhibitors (NRTIs) and one potent protease inhibitor (PI) (Table 6). Alternative regimens have been employed; these regimens include ritonavir and saquinavir (with one or two NRTIs) or nevirapine as a substitute for the PI. Dual PI therapy with ritonavir and saquinavir (hard-gel formulation), without an NRTI, appears to be potent in suppressing viremia below detectable levels and has convenient twice-daily dosing; however, the safety of this combination has not been fully established according to FDA guidelines. Also, this regimen has not been directly compared with the proven regimens of two NRTIs and a PI; thus, the Panel recommends that at least one additional NRTI be used when the physician elects to use two PIs as initial therapy. Substituting nevirapine for the PI, or using two NRTIs alone, does not achieve the goal of suppressing viremia to below detectable levels as consistently as does combination treatment with two NRTIs and a PI and should be used only if more potent treatment is not possible. However, some experts consider that there currently are insufficient data to choose between a three-drug regimen containing a PI and one containing nevirapine in the patient who has never been administered therapy; further studies are pending. Other regimens using two PIs or a PI and a non-nucleoside reverse transcriptase inhibitor (NNRTI) as initial therapy are currently in clinical trials with data pending. Of the two available NNRTIs, clinical trials support a preference for nevirapine over delavirdine based on results of viral load assays. Although 3TC is a potent NRTI when used in combination with another NRTI, in situations in which suppression of virus replication is not complete, restance to 3TC develops rapidly (*13,14*). Therefore, the optimal use for this agent is as part of a three-or-more drug combination that has a high probability of complete suppression of virus replication. Other agents in which a single genetic mutation can confer drug resistance (e.g., the NNRTIs nevirapine and delavirdine) also should be used in this manner. Use of antiretroviral agents as monotherapy is contraindicated (DI), except when no other options exist or during pregnancy to reduce perinatal transmission. When initiating antiretroviral therapy, all drugs should be started simultaneously at full dose with the following three exceptions: dose escalation regimens are recommended for ritonavir, nevirapine, and, in some cases, ritonavir plus saquinavir.

Detailed information comparing the different NRTIs, the NNRTIs, the PIs, and drug interactions between the PIs and other agents is provided (Tables 7–12). Particular attention should be paid to drug interactions between the PIs and other agents (Tables 9–12), as these are extensive and often require dose modification or substitution of various drugs. Toxicity assessment is an ongoing process; assessment at least twice during the first month of therapy and every 3 months thereafter is a reasonable management approach.

Initiating Therapy in Patients Who Have Advanced-Stage HIV Disease

All patients diagnosed as having advanced HIV disease, which is defined as any condition meeting the 1993 CDC definition of AIDS (6), should be treated with an-

tiretroviral agents regardless of plasma viral levels (AI). All patients who have symptomatic HIV infection without AIDS, defined as the presence of thrush or unexplained fever, also should be treated.

Special Considerations in the Patient Who Has Advanced-Stage HIV Disease

Some patients with OIs, wasting, dementia, or malignancy are first diagnosed with HIV infection at this advanced stage of disease. All patients who have advanced HIV disease should be treated with antiretroviral therapy. When the patient is acutely ill with an OI or other complication of HIV infection, the clinician should consider clinical issues (e.g., drug toxicity, ability to adhere to treatment regimens, drug interactions, and laboratory abnormalities) when determining the timing of initiation of antiretroviral therapy. Once therapy is initiated, a maximally suppressive regimen (e.g., two NRTIs and a PI) should be used (Table 6). Advanced-stage patients being maintained on an antiretroviral regimen should not have the therapy discontinued during an acute OI or malignancy, unless concerns exist regarding drug toxicity, intolerance, or drug interactions.

Patients who have progressed to AIDS often are treated with complicated combinations of drugs, and the clinician and patient should be alert to the potential for multiple drug interactions. Thus, the choice of which antiretroviral agents to use must be made with consideration given to potential drug interactions and overlapping drug toxicities (Tables 7–12). For instance, the use of rifampin to treat active tuberculosis is problematic in a patient who is being administered a PI, which adversely affects the metabolism of rifampin but is frequently needed to effectively suppress viral replication in these advanced patients. Conversely, rifampin lowers the blood level of PIs, which may result in suboptimal antiretroviral therapy. Although rifampin is contraindicated or not recommended for use with all of the PIs, the clinician might consider using a reduced dose of rifabutin (Tables 8–11); this topic is discussed in greater detail elsewhere (*15*). Other factors complicating advanced disease are wasting and anorexia, which may prevent patients from adhering to the dietary requirements for efficient absorption of certain protease inhibitors. Bone marrow suppression associated with ZDV and the neuropathic effects of ddC, d4T and ddI may combine with the direct effects of HIV to render the drugs intolerable. Hepatotoxicity associated with certain PIs may limit the use of these drugs, especially in patients who have underlying liver dysfunction. The absorption and half life of certain drugs may be altered by antiretroviral agents, particularly the PIs and NNRTIs whose metabolism involves the hepatic cytochrome p450 (CYP450) enzymatic pathway. Some of these PIs and NNRTIs (i.e., ritonavir, indinavir, saquinavir, nelfinavir, and delavirdine) inhibit the CYP450 pathway; others (e.g., nevirapine) induce CYP450 metabolism. CYP450 inhibitors have the potential to increase blood levels of drugs metabolized by this pathway. Adding a CYP450 inhibitor can sometimes improve the pharmacokinetic profile of selected agents (e.g., adding ritonavir therapy to the hard-gel formulation of saquinavir) as well as contribute an additive antiviral effect; however, these interactions also can result in life-threatening drug toxicity (Tables 10–12). As a result, health-care providers should inform their patients of the need to discuss any new drugs, including over-the-counter agents and alternative medications, that they may consider taking, and careful attention should be given to the relative risk versus benefits of specific combinations of agents.

Initiation of potent antiretroviral therapy often is associated with some degree of recovery of immune function. In this setting, patients who have advanced HIV disease and subclinical opportunistic infections (e.g., mycobacterium avium intracellulare [MAI] or CMV) may develop a new immunologic response to the pathogen, and, thus, new symptoms may develop in association with the heightened immunologic and/or inflammatory response. This should not be interpreted as a failure of antiretroviral therapy, and these newly presenting OIs should be treated appropriately while maintaining the patient on the antiretroviral regimen. Viral load measurement is helpful in clarifying this association.

INTERRUPTION OF ANTIRETROVIRAL THERAPY

There are multiple reasons for temporary discontinuation of antiretroviral therapy, including intolerable side effects, drug interactions, first trimester of pregnancy when the patient so elects, and unavailability of drug. There are no currently available studies and therefore no reliable estimate of the number of days, weeks or months that constitute a clinically important interruption of one or more components of a therapeutic regimen that would increase the likelihood of drug resistance. If any antiretroviral medication has to be discontinued for an extended time, clinicians and patients should be aware of the theoretical advantage of stopping all antiretroviral agents simultaneously, rather than continuing one or two agents, to minimize the emergence of resistant viral strains (see Principle 4).

CHANGING A FAILING REGIMEN

Considerations for Changing a Failing Regimen

The decision to change regimens should be approached with careful consideration of several complex factors. These factors include recent clinical history and physical examination; plasma HIV RNA levels measured on two separate occasions; absolute CD4+ T cell count and changes in these counts; remaining treatment options in terms of potency, potential resistance patterns from prior antiretroviral therapies, and potential for adherence/tolerance; assessment of adherence to medications; and psychological preparation of the patient for the implications of the new regimen (e.g., side effects, drug interactions, dietary requirements and possible need to alter concomitant medications) (see Principle 7). Failure of a regimen may occur for many reasons: initial viral resistance to one or more agents, altered absorption or metabolism of the drug, multidrug pharmacokinetics that adversely affect therapeutic drug levels, and poor patient adherence to a regimen due to either poor compliance or inadequate patient education about the therapeutic agents. In regard to the last issue, the health-care provider should carefully assess patient adherence before changing antiretroviral therapy; health-care workers involved in the care of the patient (e.g., the case manager or social worker) may be helpful in this evaluation. Clinicians should be aware of the prevalence of mental health disorders and psychoactive substance use disorders in certain HIV-infected persons; inadequate mental health treatment services may jeopardize the ability of these persons to adhere to their medical treatment.

Proper identification of and intervention in these mental health disorders can greatly enhance adherence to medical HIV treatment.

It is important to distinguish between the need to change therapy because of drug failure versus drug toxicity. In the latter case, it is appropriate to substitute one or more alternative drugs of the same potency and from the same class of agents as the agent suspected to be causing the toxicity. In the case of drug failure where more than one drug had been used, a detailed history of current and past antiretroviral medications, as well as other HIV-related medications, should be obtained. Optimally and when possible, the regimen should be changed entirely to drugs that have not been taken previously. With triple combinations of drugs, at least two and preferably three new drugs must be used; this recommendation is based on the current understanding of strategies to prevent drug resistance (see Principles 4 and 5). Assays to determine genotypic resistance are commercially available; however, these have not undergone field testing to demonstrate clinical utility and are not approved by the FDA. The Panel does not recommend these assays for routine use at present.

The following three categories of patients should be considered with regard to a change in therapy: 1) persons who are receiving incompletely suppressive antiretroviral therapy with single or double nucleoside therapy and with detectable or undetectable plasma viral load; 2) persons who have been on potent combination therapy, including a PI, and whose viremia was initially suppressed to undetectable levels but has again become detectable; and 3) persons who have been on potent combination therapy, including a PI, and whose viremia was never suppressed to below detectable limits. Although persons in these groups should have treatment regimens changed to maximize the chances of durable, maximal viral RNA suppression, the first group may have more treatment options because they are PI naive.

Criteria for Changing Therapy

The goal of antiretroviral therapy, which is to improve the length and quality of the patient's life, is likely best accomplished by maximal suppression of viral replication to below detectable levels (currently defined as <500 copies/mL) sufficiently early to preserve immune function. However, this reduction cannot always be achieved with a given therapeutic regimen, and frequently regimens must be modified. In general, the plasma HIV RNA level is the most important parameter to consider in evaluating response to therapy, and increases in levels of viremia that are substantial, confirmed, and not attributable to intercurrent infection or vaccination indicate failure of the drug regimen, regardless of changes in the CD4+ T cell counts. Clinical complications and sequential changes in CD4+ T cell count may complement the viral load test in evaluating a response to treatment. Specific criteria that should prompt consideration for changing therapy include the following:

- *Less than a 0.5–0.75 log reduction in plasma HIV RNA by 4–8 weeks following initiation of therapy (CIII).*
- *Failure to suppress plasma HIV RNA to undetectable levels within 4–6 months of initiating therapy (BIII).* The degree of initial decrease in plasma HIV RNA and the overall trend in decreasing viremia should be considered. For instance, a patient with 10^6 viral copies/mL prior to therapy who stabilizes after 6 months of therapy

at an HIV RNA level that is detectable but <10,000 copies/mL may not warrant an immediate change in therapy.

- *Repeated detection of virus in plasma after initial suppression to undetectable levels, suggesting the development of resistance (BIII)*. However, the degree of plasma HIV RNA increase should be considered; the physician may consider short-term further observation in a patient whose plasma HIV RNA increases from undetectable to low-level detectability (e.g., 500–5,000 copies/mL) at 4 months. In this situation, the patient should be monitored closely. However, most patients whose plasma HIV RNA levels become detectable after having been undetectable will subsequently show progressive increases in plasma viremia that will likely require a change in antiretroviral regimen.
- *Any reproducible significant increase, defined as threefold or greater, from the nadir of plasma HIV RNA not attributable to intercurrent infection, vaccination, or test methodology except as noted above (BIII).*
- *Undetectable viremia in the patient who is being administered double nucleoside therapy (BIII)*. Patients currently receiving two NRTIs who have achieved the goal of no detectable virus have the option of either continuing this regimen or modifying the regimen to conform to regimens in the preferred category (Table 6). Prior experience indicates that most of these patients on double nucleoside therapy will eventually have virologic failure with a frequency that is substantially greater compared with patients treated with the preferred regimens.
- *Persistently declining CD4+ T cell numbers, as measured on at least two separate occasions (see Principle 2 for significant decline) (CIII)*.
- *Clinical deterioration (DIII)*. A new AIDS-defining diagnosis that was acquired after the time treatment was initiated suggests clinical deterioration but may or may not suggest failure of antiretroviral therapy. If the antiretroviral effect of therapy was poor (e.g., a less than tenfold reduction in viral RNA), then a judgment of therapeutic failure could be made. However, if the antiretroviral effect was good but the patient was already severely immunocompromised, the appearance of a new opportunistic disease may not necessarily reflect a failure of antiretroviral therapy, but rather a persistence of severe immunocompromise that did not improve despite adequate suppression of virus replication. Similarly, an accelerated decline in CD4+ T cell counts suggests progressive immune deficiency providing there are sufficient measurements to ensure quality control of CD4+ T cell measurements.

A final consideration in the decision to change therapy is the recognition of the still limited choice of available agents and the knowledge that a decision to change may reduce future treatment options for the patient (see Principle 7). This consideration may influence the physician to be somewhat more conservative when deciding to change therapy. Consideration of alternative options should include potency of the substituted regimen and probability of tolerance of or adherence to the alternative regimen. Clinical trials have demonstrated that partial suppression of virus is superior to no suppression of virus. However, some physicians and patients may prefer to suspend treatment to preserve future options or because a sustained antiviral effect

cannot be achieved. Referral to or consultation with an experienced HIV clinician is appropriate when the clinician is considering a change in therapy. When possible, patients who require a change in an antiretroviral regimen but without treatment options that include using currently approved drugs should be referred for consideration for inclusion in an appropriate clinical trial.

Therapeutic Options When Changing Antiretroviral Therapy

Recommendations for changes in treatment differ according to the indication for the change. If the desired virologic objectives have been achieved in patients who have intolerance or toxicity, a substitution should be made for the offending drug, preferably with an agent in the same class with a different toxicity or tolerance profile. If virologic objectives have been achieved but the patient is receiving a regimen not in the preferred category (e.g., two NRTIs or monotherapy), there is the option either to continue treatment with careful monitoring of viral load or to add drugs to the current regimen to comply with preferred treatment regimens. Most experts consider that treatment with regimens not in the preferred category is associated with eventual failure and recommend the latter tactic. At present, few clinical data are available to support specific strategies for changing therapy in patients who have failed the preferred regimens that include PIs; however, several theoretical considerations should guide decisions. Because of the relatively rapid mutability of HIV, viral strains that are resistant to one or more agents often emerge during therapy, particularly when viral replication has not been maximally suppressed. Of major concern is recent evidence of broad cross-resistance among the class of PIs. Evidence indicates that viral strains that become resistant to one PI will have reduced susceptibility to most or all other PIs. Thus, the likelihood of success of a subsequently administered PI + two NRTI regimen, even if all drugs are different from the initial regimen, may be limited, and many experts would include two new PIs in the subsequent regimen.

Some of the most important guidelines to follow when changing a patient's antiretroviral therapy are summarized (Table 13), and some of the treatment options available when a decision has been made to change the antiretroviral regimen are outlined (Table 14). Limited data exist to suggest that any of these alternative regimens will be effective (Table 14), and careful monitoring and consultation with an expert in the care of such HIV-infected patients is desirable. A change in regimen because of treatment failure should ideally involve complete replacement of the regimen with different drugs to which the patient is naive. This typically would include the use of two new NRTIs and one new PI or NNRTI, two PIs with one or two new NRTIs, or a PI combined with an NNRTI. Dose modifications may be required to account for drug interactions when using combinations of PIs or a PI and NNRTI (Table 12). In some persons, these options are not possible because of prior antiretroviral use, toxicity, or intolerance. In the clinically stable patient who has detectable viremia for whom an optimal change in therapy is not possible, it may be prudent to delay changing therapy in anticipation of the availability of newer and more potent agents. It is recommended that the decision to change therapy and design a new regimen should be made with assistance from a clinician experienced in the treatment of HIV infected patients through consultation or referral.

ACUTE HIV INFECTION

Considerations for Treatment of Patients Who Have Acute HIV Infection

Various studies indicate that 50%–90% of patients acutely infected with HIV will experience at least some symptoms of the acute retroviral syndrome (Table 15) and can thus be identified as candidates for early therapy (*16*–*19*). However, acute HIV infection is often not recognized in the primary-care setting because of the similarity of the symptom complex with those of the "flu" or other common illnesses. Also, acute primary infection may occur without symptoms. Physicians should maintain a high level of suspicion for HIV infection in all patients with a compatible clinical syndrome (Table 15) and should obtain appropriate laboratory confirmation. Information regarding treatment of acute HIV infection from clinical trials is limited. There is evidence for a short-term effect of therapy on viral load and CD4+ T cell counts (*20*), but there are as yet no outcome data demonstrating a clinical benefit of antiretroviral treatment of primary HIV infection. Clinical trials completed to date also have been limited by small sample sizes, short duration of follow-up, and often by the use of treatment regimens that have suboptimal antiviral activity by current standards. However, results from these studies generally support antiretroviral treatment of acute HIV infection. Ongoing clinical trials are addressing the question of the long-term clinical benefit of more potent treatment regimens.

The theoretical rationale for early intervention (see Principle 10) is fourfold:

- to suppress the initial burst of viral replication and decrease the magnitude of virus dissemination throughout the body;
- to decrease the severity of acute disease;
- to potentially alter the initial viral "set-point", which may ultimately affect the rate of disease progression;
- to possibly reduce the rate of viral mutation due to the suppression of viral replication.

The physician and the patient should be aware that therapy of primary HIV infection is based on theoretical considerations, and the potential benefits, described above, should be weighed against the potential risks (see below). Most experts endorse treatment of acute HIV infection based on the theoretical rationale, limited but supportive clinical trial data, and the experience of HIV clinicians.

The risks associated with therapy for acute HIV infection include adverse effects on quality of life resulting from drug toxicities and dosing constraints; the potential, if therapy fails to effectively suppress viral replication, for the development of drug resistance that may limit future treatment options; and the potential need for continuing therapy indefinitely. These considerations are similar to those for initiating therapy in the asymptomatic patient (see Considerations in Initiating Therapy in the Asymptomatic HIV-infected Patient).

Deciding Whom to Treat During Acute HIV Infection

Many experts would recommend antiretroviral therapy for all patients who demonstrate laboratory evidence of acute HIV infection (AII). Such evidence includes HIV RNA in plasma that can be detected by using sensitive PCR or bDNA assays together with a negative or indeterminate HIV antibody test. Although measurement of plasma HIV RNA is the preferable method of diagnosis, a test for p24 antigen may be useful when RNA testing is not readily available. However, a negative p24 antigen test does not rule out acute infection. When suspicion for acute infection is high (e.g., as in a patient who has a report of recent risk behavior in association with suggestive symptoms and signs [Table 15]), a test for HIV RNA should be performed (BII).* Persons may or may not have symptoms of the acute retroviral syndrome. Viremia occurs acutely after infection before the detection of a specific immune response; an indeterminate antibody test may occur when a person is in the process of seroconversion.

Apart from patients who have acute primary HIV infection, many experts also would consider therapy for patients in whom seroconversion has been documented to have occurred within the previous 6 months (CIII). Although the initial burst of viremia in infected adults has usually resolved by 2 months, treatment during the 2–6–month period after infection is based on the likelihood that virus replication in lymphoid tissue is still not maximally contained by the immune system during this time. Decisions regarding therapy for patients who test antibody positive and who believe the infection is recent but for whom the time of infection cannot be documented should be made using the Asymptomatic HIV Infection algorithm mentioned previously (CIII). No patient should be treated for HIV infection until the infection is documented, except in the setting of post-exposure prophylaxis of health-care workers with antiretroviral agents (*21*)†. All patients without a formal medical record of a positive HIV test (e.g., persons who have tested positive by available home testing kits) should be tested by both the ELISA and an established confirmatory test (e.g., the Western Blot) to document HIV infection (AI).

Treatment Regimen for Primary HIV Infection

Once the physician and patient have decided to use antiretroviral therapy for primary HIV infection, treatment should be implemented with the goal of suppressing plasma HIV RNA levels to below detectable levels (AIII). The weight of current experience suggests that the therapeutic regimen for acute HIV infection should include a combination of two NRTIs and one potent PI (AII). Although most experience to date with PIs in the setting of acute HIV infection has been with ritonavir, indinavir or nelfinavir (*2,22–24*), insufficient data are available to make firm conclusions regarding specific drug recommendations. Potential combinations of agents available are much the same as those used in established infection (Table 6). These aggressive regimens may be associated with several disadvantages (e.g., drug toxicity, large numbers of pills, cost of drugs, and the possibility of developing drug resistance that may limit future options); the latter is likely if virus replication is not adequately suppressed or if the patient has been infected with a viral strain that is already resistant to one or more

*Patients diagnosed with HIV infection by HIV RNA testing should have confirmatory testing performed (Table 2).
†Or treatment of neonates born to HIV-infected mothers.

agents. The patient should be carefully counseled regarding these potential limitations and individual decisions made only after weighing the risks and sequelae of therapy against the theoretical benefit of treatment.

Any regimen that is not expected to maximally suppress viral replication is not considered appropriate for treating the acutely HIV-infected person (EIII) because a) the ultimate goal of therapy is suppression of viral replication to below the level of detection, b) the benefits of therapy are based primarily on theoretical considerations, and c) long-term clinical outcome benefit has not been documented. Additional clinical studies are needed to delineate further the role of antiretroviral therapy in the primary infection period.

Patient Follow-up

Testing for plasma HIV RNA levels and CD4+ T cell count and toxicity monitoring should be performed as previously described in Use of Testing for Plasma HIV RNA levels and CD4+ T Cell Count in Guiding Decisions for Therapy, that is, on initiation of therapy, after 4 weeks, and every 3–4 months thereafter (AII). Some experts suggest that testing for plasma HIV RNA levels at 4 weeks is not helpful in evaluating the effect of therapy for acute infection because viral loads may be decreasing from peak viremia levels even in the absence of therapy.

Duration of Therapy for Primary HIV Infection

Once therapy is initiated, many experts would continue to treat the patient with antiretroviral agents indefinitely because viremia has been documented to reappear or increase after discontinuation of therapy (CII). However, some experts would treat for one year and then reevaluate the patient with CD4+ T cell determinations and quantitative HIV RNA measurements. The optimal duration and composition of therapy are unknown, and ongoing clinical trials are expected to provide data relevant to these issues. The difficulties inherent in determining the optimal duration and composition of therapy initiated for acute infection should be considered when first counseling the patient regarding therapy.

CONSIDERATIONS FOR ANTIRETROVIRAL THERAPY IN THE HIV-INFECTED ADOLESCENT

HIV-infected adolescents who were infected through sexual contact or through injecting-drug use during adolescence appear to follow a clinical course that is more similar to HIV disease in adults than in children. In contrast, adolescents who were infected perinatally or through blood products as young children have a unique clinical course that may differ from other adolescents and long-term surviving adults. Currently, most HIV-infected adolescents were infected through sexual contact during the adolescent period and are in a relatively early stage of infection, making them ideal candidates for early intervention.

Puberty is a time of somatic growth and hormonally mediated changes, with females developing more body fat and males more muscle mass. Although theoretically these physiologic changes could affect drug pharmacology, particularly in the case of drugs with a narrow therapeutic index that are used in combination with protein-

bound medicines or hepatic enzyme inducers or inhibitors, no clinically substantial impact of puberty on the use of NRTIs has been observed. Clinical experience with PIs and NNRTIs has been limited. Thus, it is currently recommended that medications used to treat HIV and OIs in adolescents should be administered in a dosage based on Tanner staging of puberty and not specific age. Adolescents in early puberty (Tanner I–II) should receive doses as recommended in the pediatric guidelines, whereas those in late puberty (Tanner V) should receive doses recommended in the adult guidelines. Youth who are in the midst of their growth spurt (Tanner III females and Tanner IV males) should be closely monitored for medication efficacy and toxicity when choosing adult or pediatric dosing guidelines.

CONSIDERATIONS FOR ANTIRETROVIRAL THERAPY IN THE PREGNANT HIV-INFECTED WOMAN

Guidelines for optimal antiretroviral therapy and for initiation of therapy in pregnant HIV-infected women should be the same as those delineated for nonpregnant adults (see Principle 8). Thus, the woman's clinical, virologic, and immunologic status should be the primary factor in guiding treatment decisions. However, it must be realized that the potential impact of such therapy on the fetus and infant is unknown. The decision to use any antiretoviral drug during pregnancy should be made by the woman following discussion with her health-care provider regarding the known and unknown benefits and risks to her and her fetus. Long-term follow-up is recommended for all infants born to women who have received antiretroviral drugs during pregnancy.

Women who are in the first trimester of pregnancy and who are not receiving antiretroviral therapy may wish to consider delaying initiation of therapy until after 10–12 weeks' gestation because this is the period of organogenesis when the embryo is most susceptible to potential teratogenic effects of drugs; the risks of antiretroviral therapy to the fetus during that period are unknown. However, this decision should be carefully considered and discussed between the health-care provider and the patient and should include an assessment of the woman's health status and the potential benefits and risks of delaying initiation of therapy for several weeks. If clinical, virologic, or immunologic parameters are such that therapy would be recommended for nonpregnant persons, many experts would recommend initiating therapy, regardless of gestational age. Nausea and vomiting in early pregnancy, which affect the ability to adequately take and absorb oral medications, may be a factor in deciding whether to administer treatment during the first trimester.

Some women already receiving antiretroviral therapy may have their pregnancy diagnosed early enough in gestation that concern for potential teratogenicity may lead them to consider temporarily stopping antiretroviral therapy until after the first trimester. Insufficient data exist that either support or refute teratogenic risk of antiretroviral drugs when administered during the first 10–12 weeks' gestation. However, a rebound in viral levels would be anticipated during the period of discontinuation, and this rebound could theoretically be associated with increased risk of early in utero HIV transmission or could potentiate disease progression in the woman (*25*). Although the effects of all antiretroviral drugs on the developing fetus during the first trimester are uncertain, most experts recommend continuation of a maximally sup-

pressive regimen even during the first trimester. If antiretroviral therapy is discontinued during the first trimester for any reason, all agents should be stopped simultaneously to avoid development of resistance. Once the drugs are reinstituted, they should be introduced simultaneously for the same reason.

The choice of which antiretroviral agents to use in pregnant women is subject to unique considerations (see Principle 8). Currently, minimal data are available regarding the pharmacokinetics and safety of antiretroviral agents during pregnancy for drugs other than ZDV. In the absence of data, drug choice needs to be individualized based on discussion with the patient and available data from preclinical and clinical testing of the individual drugs. The FDA pregnancy classification for all currently approved antiretroviral agents and selected other information relevant to the use of antiretroviral drugs in pregnancy is provided (Table 16). The predictive value of in vitro and animal-screening tests for adverse effects in humans is unknown. Many drugs commonly used to treat HIV infection or its consequences may have positive findings on one or more of these screening tests. For example, acyclovir is positive on some in vitro assays for chromosomal breakage and carcinogenicity and is associated with some fetal abnormalities in rats; however, data on human experience from the Acyclovir in Pregnancy Registry indicate no increased risk of birth defects to date in infants with in utero exposure to acyclovir (*26*).

Of the currently approved nucleoside analogue antiretroviral agents, the pharmacokinetics of only ZDV and 3TC have been evaluated in infected pregnant women to date (*27,28*). Both drugs seem to be well tolerated at the usual adult doses and cross the placenta, achieving concentrations in cord blood similar to those observed in maternal blood at delivery. All the nucleosides except ddI have preclinical animal studies that indicate potential fetal risk and have been classified as FDA pregnancy category C (Table 16); ddI has been classified as category B. In primate studies, all the nucleoside analogues seem to cross the placenta, but ddI and ddC apparently have significantly less placental transfer (fetal to maternal drug ratios of 0.3 to 0.5) than do ZDV, d4T, and 3TC (fetal to maternal drug ratios >0.7) (*29*).

Of the NNRTIs, only nevirapine administered once at the onset of labor has been evaluated in pregnant women. The drug was well tolerated after a single dose and crossed the placenta and achieved neonatal blood concentrations equivalent to those in the mother. The elimination of nevirapine administered during labor in the pregnant women in this study was prolonged (mean half-life following a single dose, 66 hours) compared with nonpregnant persons (mean half-life following a single dose, 45 hours). Data on multiple dosing during pregnancy are not yet available. Delavirdine has not been studied in Phase I pharmacokinetic and safety trials in pregnant women. In premarketing clinical studies, outcomes of seven unplanned pregnancies were reported. Three of these were ectopic pregnancies, and three resulted in healthy live births. One infant was born prematurely, with a small ventricular septal defect, to a patient who had received approximately 6 weeks of treatment with delavirdine and ZDV early in the course of pregnancy.

Although studies of combination therapy with protease inhibitors in pregnant HIV-infected women are in progress, no data are currently available regarding drug dosage, safety and tolerance during pregnancy. In mice, indinavir has substantial placental passage; however, in rabbits, little placental passage was observed. Ritonavir has been demonstrated to have some placental passage in rats. There are some spe-

cial theoretical concerns regarding the use of indinavir late in pregnancy. Indinavir is associated with side effects (hyperbilirubinemia and renal stones) that theoretically could be problematic for the newborn if transplacental passage occurs and the drug is administered shortly before delivery. These side effects are particularly problematic because the immaturity of the metabolic enzyme system of the neonatal liver would likely be associated with prolonged drug half-life leading to extended drug exposure in the newborn that could lead to potential exacerbation of physiologic neonatal hyperbilirubinemia. Because of immature neonatal renal function and the inability of the neonate to voluntarily ensure adequate hydration, high drug concentrations and/or delayed elimination in the neonate could result in a higher risk for drug crystallization and renal stone development than observed in adults. These concerns are theoretical and such effects have not been reported; because the half-life of indinavir in adults is short, these concerns may only be relevant if drug is administered near the time of labor. Gestational diabetes is a pregnancy-related complication that can develop in some women; administration of any of the four currently available protease inhibitors has been associated with new onset diabetes mellitus, hyperglycemia, or exacerbation of existing diabetes mellitus in HIV-infected patients (*30*). Pregnancy is itself a risk factor for hyperglycemia, and it is unknown if the use of protease inhibitors will exacerbate this risk for hyperglycemia. Health-care providers caring for infected pregnant women who are being administered PI therapy should be aware of the possibility of hyperglycemia and closely monitor glucose levels in their patients and instruct their patients on how to recognize the early symptoms of hyperglycemia.

To date, the only drug that has been shown to reduce the risk of perinatal HIV transmission is ZDV when administered according to the following regimen: orally administered antenatally after 14 weeks' gestation and continued throughout pregnancy, intravenously administered during the intrapartum period, and administered orally to the newborn for the first 6 weeks of life (*31*). This chemoprophylactic regimen was shown to reduce the risk for perinatal transmission by 66% in a randomized, double-blind clinical trial, pediatric ACTG 076 (*32*). Insufficient data are available to justify the substitution of any antiretroviral agent other than ZDV to reduce perinatal HIV transmission; further research should address this question. For the time being, if combination antiretroviral drugs are administered to the pregnant woman for treatment of her HIV infection, ZDV should be included as a component of the antenatal therapeutic regimen whenever possible, and the intrapartum and neonatal ZDV components of the chemoprophylactic regimen should be administered to reduce the risk for perinatal transmission. If a woman is not administered ZDV as a component of her antenatal antiretroviral regimen (e.g., because of prior history of nonlife-threatening ZDV-related severe toxicity or personal choice), intrapartum and newborn ZDV should continue to be recommended; when use of ZDV is contraindicated in the woman, the intrapartum component may be deleted, but the newborn component is still recommended. ZDV and d4T should not be administered together due to potential pharmacologic antagonism. When d4T is a preferred nucleoside for treatment of a pregnant woman, it is recommended that antenatal ZDV not be added to the regimen; however, intrapartum and neonatal ZDV should still be given.

The time-limited use of ZDV alone during pregnancy for chemoprophylaxis of perinatal transmission is controversial. The potential benefits of standard combination antiretroviral regimens for treatment of HIV infection should be discussed with and

offered to all pregnant HIV-infected women. Some women may wish to restrict exposure of their fetus to antiretroviral drugs during pregnancy but still wish to reduce the risk of transmitting HIV to their infant. For women in whom initiation of antiretroviral therapy for treatment of their HIV infection would be considered optional (e.g., CD4+ count >500/mm^3 and plasma HIV RNA <10,0000–20,000 RNA copies/mL), time-limited use of ZDV during the second and third trimesters of pregnancy is less likely to induce the development of resistance due to the limited viral replication existing in the patient and the time-limited exposure to the antiretroviral drug. For example, the development of resistance was unusual among the healthy population of women who participated in Pediatric (P)-ACTG 076 (*33*). The use of ZDV chemoprophylaxis alone during pregnancy might be an appropriate option for these women. However, for women who have more advanced disease and/or higher levels of HIV RNA, concerns about resistance are greater and these women should be counseled that a combination antiretroviral regimen that includes ZDV for reducing transmission risk would be more optimal for their own health than use of ZDV chemoprophylaxis alone.

Monitoring and use of HIV-1 RNA for therapeutic decision making during pregnancy should be performed as recommended for nonpregnant persons. Transmission of HIV from mother to infant can occur at all levels of maternal HIV-1 RNA. In untreated women, higher HIV-1 RNA levels correlate with increased transmission risk. However, in ZDV-treated women this relationship is markedly attenuated (*32*). ZDV is effective in reducing transmission regardless of maternal HIV RNA level. Therefore, the use of the full ZDV chemoprophylaxis regimen, including intravenous ZDV during delivery and the administration of ZDV to the infant for the first 6 weeks of life, alone or in combination with other antiretrovirals, should be discussed with and offered to all infected pregnant women regardless of their HIV-1 RNA level. Health-care providers who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to antiretroviral drugs (either administered alone or in combinations) to the Antiretroviral Pregnancy Registry. The registry collects observational, nonexperimental data regarding antiretroviral exposure during pregnancy for the purpose of assessing potential teratogenicity. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The registry is a collaborative project with an advisory committee of obstetric and pediatric practitioners, staff from CDC and NIH, and staff from pharmaceutical manufacturers. The registry allows the anonymity of patients, and birth outcome follow-up is obtained by registry staff from the reporting physician. Referrals should be directed to Antiretroviral Pregnancy Registry, Post Office Box 13398, Research Triangle Park, NC 27709-3398; telephone (800) 258-4263.

CONCLUSION

The Panel has attempted to use the advances in current understanding of the pathogenesis of HIV in the infected person to translate scientific principles and data obtained from clinical experience into recommendations that can be used by the clinician and patient to make therapeutic decisions. The recommendations are offered in the context of an ongoing dialogue between the patient and the clinician after having defined specific therapeutic goals with an acknowledgment of uncertainties. It is nec-

essary for the patient to receive a continuum of medical care and services, including social, psychosocial, and nutritional services, with the availability of expert referral and consultation. To achieve the maximal flexibility in tailoring therapy to each patient over the duration of his or her infection, it is imperative that drug formularies allow for all FDA-approved NRTI, NNRTI, and PI as treatment options. The Panel strongly urges industry and the public and private sectors to conduct further studies to allow refinement of these guidelines. Specifically, studies are needed to optimize recommendations for first-line therapy; to define second-line therapy; and to more clearly delineate the reason(s) for treatment failure. The Panel remains committed to revising their recommendations as such new data become available.

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MORBIDITY AND MORTALITY
WEEKLY REPORT

Resurgent Bacterial Sexually Transmitted Disease Among Men Who Have Sex With Men — King County, Washington, 1997–1999

During the late 1980s and early 1990s, King County, Washington (1998 population: 1.6 million), experienced a substantial epidemic of infectious syphilis (i.e., primary, secondary, and early latent). Subsequently, reported cases of infectious syphilis declined to six cases in 1995 and one in 1996; five of the 1995 cases and the case in 1996 were believed to have been acquired outside King County. However, in 1997, sustained spread of syphilis was reestablished in King County (*1*). To determine whether this reemergence was associated with changes in the epidemiology of other sexually transmitted diseases (STDs), Public Health–Seattle and King County (PHSKC) analyzed notifiable STD data for 1997–1999. This report summarizes the results of this analysis, which indicate that infectious syphilis among men who have sex with men (MSM) in King County increased to 46 cases during January–June 1999, and chlamydia and gonorrhea also increased among MSM attending public health clinics.

For this report, PHSKC analyzed surveillance data on infectious syphilis, chlamydia, and gonorrhea reported to PHSKC from health-care providers and laboratories. Data included disease, sex, stage of disease, racial/ethnic group, age, and in some cases sexual orientation and anatomic site of infection. Persons with these diseases were interviewed by PHSKC staff for partner management. Data collected included number and sex of sex partners, sexual orientation, and other risk factors.

Syphilis cases increased steadily from late 1997 to mid-1998, appeared to stabilize in the second half of 1998, then increased during January–June 1999 (Figure 1). The proportion of cases in MSM increased from 21% (four of 19) in 1997 to 85% (75 of 88) in 1998 and 1999 ($p<0.01$). Among 79 MSM, the median age was 35 years (range: 19–56 years) and 70% were aged >30 years. Primary, secondary, and early latent infection accounted for 23%, 61%, and 16% of cases in MSM, respectively; these proportions did not differ significantly from 1997 to 1999. Among the 79 MSM with early latent syphilis in 1997 through June 1999, 48 (72%) of 67 had human immunodeficiency virus (HIV) infection and two others were HIV seropositive near the time syphilis was diagnosed.

From 1997 through June 1999, laboratory-confirmed infections with *Neisseria gonorrhoeae* and *Chlamydia trachomatis* among MSM attending the PHSKC STD clinic also increased (Figure 2). In addition, cases of rectal gonococcal infection in

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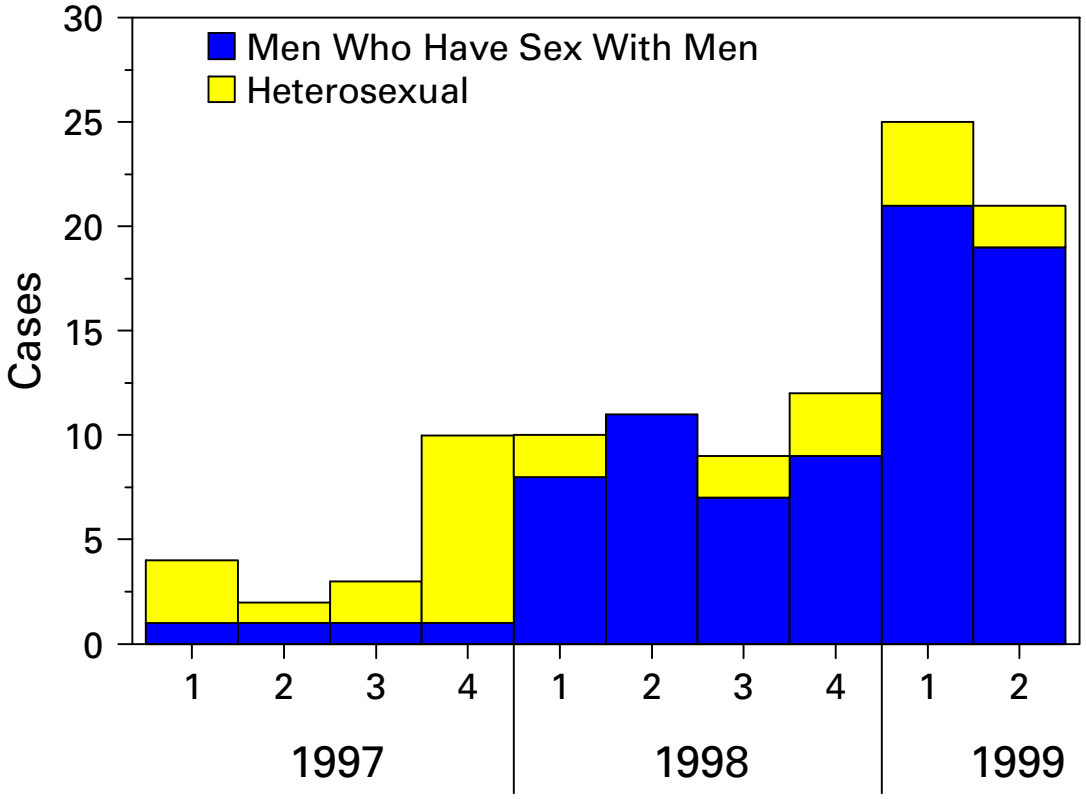
FIGURE 1. Reported cases of infectious (i.e., primary, secondary, and early latent) syphilis, by quarter and sexual orientation of infected persons — King County, Washington, 1997–1999



males reported by providers outside the STD clinic increased from six cases in 1997 to 25 cases in 1998 and 13 cases during January–June 1999. The median age of the 427 MSM who received a diagnosis of gonorrhea or chlamydial infection in the STD clinic from 1997 through June 1999 was 32 years (range: 20–53 years), and 17% with chlamydial infection and 19% with gonorrhea were known to be infected with HIV; this proportion did not vary significantly through the period of analysis.

Data on sex partners were provided by 63 (80%) of the 79 MSM with infectious syphilis from 1997 through June 1999. During the interval when syphilis was likely to have been acquired or transmitted (mean: 6 months), these men reported 740 sex partners, of whom 653 (88%) were met at anonymous venues such as bath houses, bars, or clubs; 50 (79%) of 63 men had had at least one anonymous partner (median: three partners; range: one to 100). MSM with gonorrhea or chlamydial infection reported a mean of 3.5 sex partners during the 2 months before treatment, and approximately 20% apparently acquired infection from anonymous partners.

Based on an estimate of PHSKC that 40,000 MSM reside in King County, the annual rate of infectious syphilis per 100,000 MSM increased from zero in 1996 to approximately 10 in 1997 and 90 in 1998, and the projected annual incidence in 1999 is 200 cases per 100,000. An estimated 10% of MSM in King County are infected with HIV (PHSKC, unpublished data, 1999). If 4000 HIV-infected MSM reside in King County, the projected annual incidence of infectious syphilis in the HIV-infected MSM

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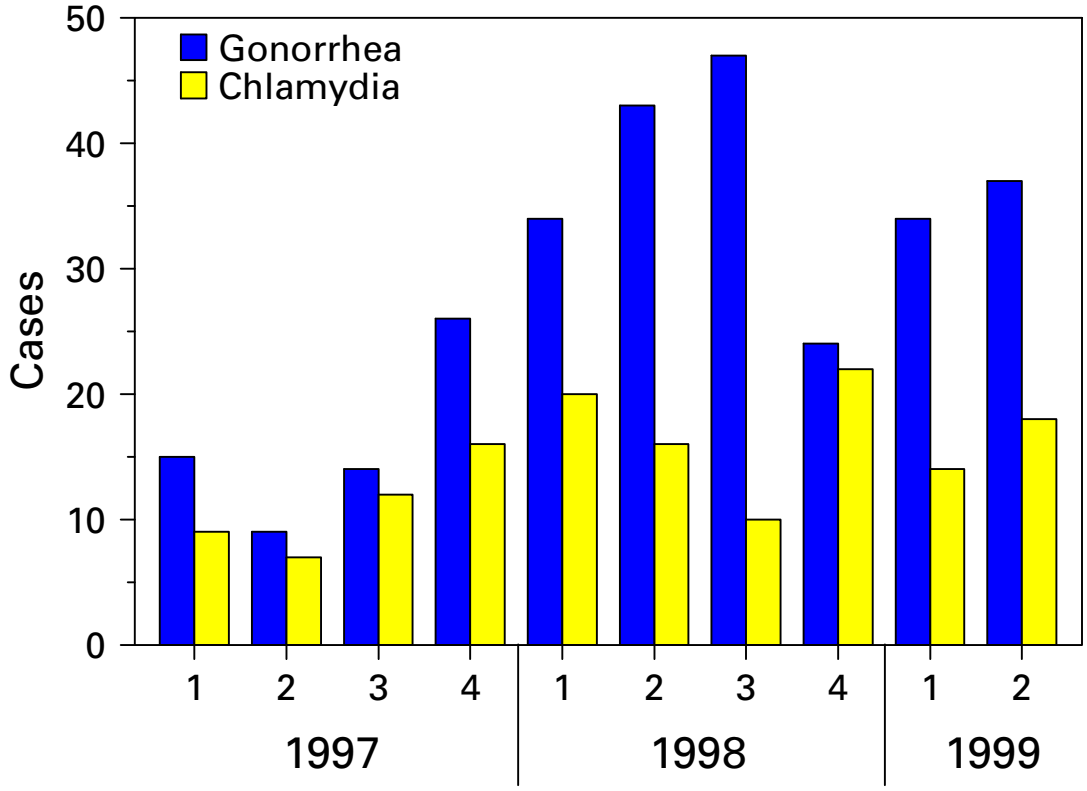
FIGURE 2. Reported cases of laboratory-confirmed gonorrhea and chlamydial infection among men who have sex with men attending a Public Health Seattle and King County STD clinic, by quarter — King County, Washington, 1997–1999



population in 1999 is approximately 1500 per 100,000. The minimum incidence of gonorrhea in MSM, based on the number of cases diagnosed in the PHSKC STD clinic plus rectal infections in males diagnosed elsewhere (data on sexual orientation are not available outside the STD clinic), increased from 180 per 100,000 MSM in 1997 to 430 and 420 in 1998 and 1999, respectively. In comparison, the reported rate of gonorrhea in presumptively heterosexual persons in King County was 50 per 100,000 in 1997 and 1998.

PHSKC has used outreach activities, targeted publications in the local gay press, and community forums to encourage MSM to follow safer sex practices and to be screened for STDs. STD and HIV testing and counseling are being offered at bath houses and other venues, screening has been expanded among MSM attending public clinics, and King County health-care providers have been encouraged to expand STD screening among at-risk MSM.

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Editorial Note: The incidence of STDs among MSM declined substantially during the early 1980s as a result of a decrease in sexual risk behavior (*2,3*). However, high-risk behaviors and STDs among MSM have increased in some cities (*4,5*). In Washington, the proportion of cases of primary and secondary syphilis among MSM declined from

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81% in 1973 to 8% in 1988 (*3*). The findings in this report indicate that syphilis transmission in King County is occurring predominantly among MSM. When STDs are introduced into a community, the size of the subsequent outbreak depends on the sexual mixing patterns of the community, the numbers of sex partners, concurrency of sexual partnerships, condom use, and the frequency of partner change (*3,6*). In King County, syphilis, gonorrhea, and chlamydia apparently have been introduced into a population of MSM who have large numbers of anonymous partners, which can result in rapid and extensive transmission of STDs (*7*). In addition to this outbreak, recent reports have suggested increases in gonococcal infection in several western states and in the frequency of unprotected anal sex among MSM (*4,5*). Some MSM may be recruiting sex partners in anonymous venues more often now than in the recent past (*8*).

The high proportion of persons with syphilis, gonorrhea, and chlamydial infection who also were infected with HIV is of particular concern. Persons with STDs, including genital ulcer disease and nonulcerative STD, have a twofold to fivefold increased risk for HIV infection (*9,10*). Control of STDs is a central component of HIV infection prevention efforts in the United States (*10*); resurgence of bacterial STD threatens national HIV infection prevention efforts.

Reasons for the increasing rates of bacterial STD in MSM in King County are unknown but may include an increased frequency of unprotected sex among some MSM. Anecdotal reports by MSM with bacterial STDs suggest that such behaviors are linked to sex with anonymous partners in bath houses, which may be related to improvements in the treatment of HIV infection or to changing patterns of recreational drug use. The age distribution of syphilis cases suggests that in King County, relapse in sexual safety among older MSM is a more important determinant than failure of young, newly sexually active MSM to adopt safer sex practices.

The findings in this report are subject to at least three limitations. First, reporting of STDs is incomplete, which could result in an underestimate of the incidence of disease in this population. Second, MSM attending STD clinics probably are not representative of all MSM at risk. Finally, some persons may not have given accurate responses when asked about sexual relationships, HIV serostatus, or high-risk behaviors.

PHSKC has employed several control measures to contain these outbreaks. Although partner notification is effective for the known partners of persons with syphilis and gonorrhea, its ability to reach exposed persons is greatly limited in situations such as the syphilis outbreak in King County, where 88% of partners were met at venues where anonymous sex is common. The high frequency of anonymous sex strongly suggests that sex partner management services for identifiable partners alone would be insufficient to control the outbreak. Print media, public service announcements, outreach, and expanded screening have been used in this outbreak to augment traditional partner management services. These interventions may have encouraged timely symptom recognition and health-seeking behavior by infected men. Among men with syphilis, 72% knew they were HIV positive and many were receiving health care for the disease, indicating that enhanced STD prevention efforts may be needed for HIV-infected MSM in health-care settings and other venues. This outbreak demonstrates the need to sustain surveillance for STDs even after rates have decreased in a community.

Bacterial Sexually Transmitted Disease — Continued

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Inadvertent Use of Bicillin® C-R for Treatment of Syphilis — Maryland, 1998

In October 1998, the Maryland Department of Health and Mental Hygiene (MDH) was notified that a public sexually transmitted disease (STD) clinic in a county (county A) had used a nonrecommended preparation to treat syphilis patients during January–October 1998. The clinic had been inadequately treating syphilis patients or syphilis contacts with Bicillin®* C-R (a mixture of 1.2 million units [MU] benzathine penicillin G [BPG] and 1.2 MU procaine penicillin G), rather than with Bicillin® L-A (2.4 MU BPG). Compared with short-acting procaine penicillin G, BPG has a longer half-life considered essential for effective syphilis treatment because it yields sustained spirochetecidal levels needed to treat the slowly reproducing agent of syphilis, *Treponema pallidum*. The inadvertent use of Bicillin C-R, which contains only half the recommended dose of BPG for syphilis, was recognized by a health-care provider at the STD clinic in a neighboring county (county B) approximately 1 month after county B had borrowed BPG from county A. This report summarizes the investigation of the use of Bicillin C-R to treat STD patients in county A and discusses the frequency of Bicillin C-R use in STD clinics nationwide. Findings of this investigation indicate that inadvertent Bicillin C-R use is more frequent than previously known and that preventive measures should be taken to minimize such use.

Three BPG-containing products are marketed by Wyeth-Ayerst Laboratories (Philadelphia, Pennsylvania): Bicillin L-A, Bicillin C-R, and Bicillin® C-R 900/300 (a mixture of 0.9 MU BPG and 0.3 MU procaine penicillin G). Besides having similar proprietary names, the package and label for Bicillin C-R and Bicillin L-A have similar lettering and colors. Bicillin L-A is recommended for treating syphilis patients and upper respiratory tract infections caused by susceptible streptococci (*1*). The efficacy of Bicillin C-R to

*Use of trade names and commercial sources is for identification only and does not imply endorsement by CDC or the U.S. Department of Health and Human Services.

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